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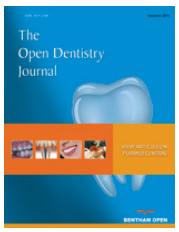

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REVIEW ARTICLE

An Update on the Mechanisms of Phenytoin Induced Gingival Overgrowth

Fathima Fazrina Farook[1,2,*], Mohamed Nuzaim M. Nizam[3] and Abdulsalam Alshammari[1,2]

[1]*Department of Preventive Dental Science, College of Dentistry, King Saud Bin Abdul Aziz University for Health Sciences, Riyadh, Saudi Arabia*
[2]*King Abdullah International Medical Research Centre, Riyadh, Saudi Arabia*
[3]*Department of Obstetrics and Gynecology, University of Malaya, Kuala Lumpur, Malaysia*

Abstract:

Background:

Phenytoin induced gingival overgrowth, a side effect with multifactorial aetiology, is characterized by an increase in the volume of extracellular tissues, particularly collagenous components, with varying degrees of inflammation.

Objective:

The aim of this paper is to review the available literature regarding the pathophysiological mechanisms of phenytoin induced gingival overgrowth.

Methods:

A thorough literature search of the PubMed/ Embase/ Web of science/ Cochrane central database was conducted to identify the mechanisms involved in the process of phenytoin-induced gingival overgrowth using the following keywords: Phenytoin; Anticonvulsant; Gingival Overgrowth; Gingival Enlargement, Gingival Hyperplasia; Drug Induced Gingival Enlargement; Drug Induced Gingival Overgrowth

Results:

According to the available evidence, several mechanisms have been proposed addressing the pathophysiological mechanism of phenytoin induced gingival overgrowth both at a cellular and molecular level. Evidence suggests that the inflammatory changes in the gingival tissues orchestrate the interaction between phenytoin and fibroblasts particularly resulting in an increase in the extracellular matrix content.

Conclusion:

However, the mechanism of production of inflammatory mediators is not fully understood. This, together with the high prevalence of Phenytoin induced gingival overgrowth, warrants further research in this area in order to develop treatment and preventive strategies for the management of this condition.

Keywords: Anticonvulsant, Gingival overgrowth, Gingival enlargement, Phenytoin, Drug induced gingival enlargement, Drug induced gingival overgrowth.

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1. INTRODUCTION

Gingival Enlargement (GE) or Gingival Overgrowth (GO) is a clinical condition that alters the position of the gingival margin and comprises an increase in the size of the gingiva [1]. GO was previously described as hypertrophic gingivitis or gingival hyperplasia. Nevertheless, "gingival hyperplasia" is a misnomer as enlargement is rather an increase in extracellular tissue volume and not an increase in the number of cells [2]. It may be caused due to plaque induced inflammatory conditions, medications [3, 4], hereditary causes and systemic diseases [5 - 7].

Medication induced gingival overgrowth, is an unwanted side effect of systemic medication on periodontal tissues [7]. It was reported in the early 1960's in dental literature and is sometimes referred to as "Drug Induced Gingival enlargement or Overgrowth" or "DIGO" [7, 8]. The three drugs most frequently implicated are phenytoin, calcium channel blockers such as nifedipine [9], amlodipine, and verapamil [10] and lastly, an immune-suppressant, cyclosporine [11, 12]. Gingival overgrowth is a well-known and established side effect of phenytoin [13 - 15]. Other drugs for example sodium valproate

* Address correspondence to this author at Department of Preventive Dental Science, King Saud Bin Abdulaziz University for Health Sciences, 11426 Riyadh, Saudi Arabia / King Abdullah International Medical Research Centre, Riyadh, Saudi Arabia; E-mail: fazrinaf@ksau-hs.edu.sa

[16] and erythromycin [17] have been implicated in case reports, but the occurrence is rare [18].

In terms of prevalence, phenytoin, cyclosporine and calcium channel blockers account for 50%, 30% and 10-20% of drug induced gingival overgrowth, respectively [13, 19, 20]. However, the prevalence varies significantly and depends upon the population being investigated [21]. The stated figures do not take into account the severity of the overgrowth. Various risk factors have been identified for drug induced gingival overgrowth, such as age (children and teenagers) [15], demographic variables, drug variables, periodontal variables [22], genetic factors and concomitant medication [23].

Phenytoin, introduced in 1938, is now an established and effective treatment of acute repetitive seizures, partial-onset and generalized tonic-clonic seizures and status epilepticus [24]. Phenytoin was later used as an antiarrhythmic drug in cardiology [25]. However, currently, its usage as antiarrhythmic purpose is abandoned, but still reserves their importance in the treatment of epilepsy [24, 26].

Considering the fact that it is a major first-line antiepileptic drug (AED) in the treatment of partial and secondarily generalized seizures, it is important to know the mechanisms of phenytoin induced gingival overgrowth in order to minimize the occurrence of this adverse effect. A comprehensive understanding of the pathogenesis of this unwanted side effect is mandatory to develop suitable regimens for its management [23, 27].

As of now, in the literature several studies have aimed to ascertain the pathogenesis of drug-induced GO. However, the trigger mechanisms for such conditions are yet inconclusive. Therefore, the aim of this work was to revisit the most relevant studies published about phenytoin-induced gingival overgrowth and outline the possible mechanisms associated with this condition.

A literature search of the PubMed/ Embase/ Web of science/ Cochrane central database was conducted to identify the mechanisms involved in the process of phenytoin-induced gingival overgrowth with no time or language restriction.

2. MECHANISMS OF PHENYTOIN INDUCED GINGIVAL OVERGROWTH

Gingival overgrowth, the enlargement of gingival tissues, is due to an increase in the Extracellular Matrix (ECM) content or increase in the number of cells or both1. Increase in the ECM content could be due to increased production or reduced degradation or a combination. An increase in the number of cells may be due to increased proliferation or reduced apoptosis or both. In gingival overgrowth, the expression of genes related to these mechanisms are either increased or decreased. Inflammatory mediators play a major role in altering the expression of the genes related to gingival overgrowth [4]. Some studies have shown that phenytoin decreases the production of ECM and therefore decreases collagen synthesis [28], confirmed by a reduction in mRNA expression of type I and type III collagen. It is evident that gingival overgrowth is due to the impairment in the balance between synthesis and degradation of ECM [20, 28]. Phenytoin enhances the production of inflammatory mediators [29]. Salivary secretion of unbound phenytoin is 10% of the level in the blood. In addition, dental plaque contains phenytoin and its primary metabolite, the para-hydroxyl form [2]. A high concentration of phenytoin and lower tissue levels of the para-hydroxyl metabolite increases the severity of the gingival overgrowth [2].

Phenytoin in the saliva is absorbed or diffused *via* the sulcular epithelium into the serum causing a double exposure to phenytoin via two pathways, mainly from the systemic circulation and partly from the reabsorption pathway of the saliva. Thus, gingival sulcular tissue is more susceptible to the effects of phenytoin causing gingival overgrowth [30]. However, currently, the sources and the mechanisms of the production of inflammatory mediators in the gingival overgrowth tissues are unclear [30].

Gingival tissue is in a constant state of injury and repair. This results in an increase in chemical mediators such as cytokines, chemokines and an abundance of inflammatory cells [28, 29]. Another possible mechanism is phenytoin related stimulation in the growth of microorganisms such as *Bacteroides, actinomyces, Prevotella intermedia, Porphyromonas gingivalis and Treponema denticola* and fusiform bacteria [28]. These organisms produce established dental plaque biofilms aggravating the inflammatory process [28, 29]. The abundant inflammatory mediators contribute to the gingival overgrowth. Phenytoin is known to cause folate deficiencies locally or systemically. Folate is necessary for many vital cellular functions such as nucleic acid metabolism and cell proliferation. As a result, phenytoin induced folate deficiency can cause degenerative changes in gingival epithelium. Degenerative materials induce an inflammatory response [4].

The immune system could be stimulated by the drug phenytoin via mechanisms including the induction of lymphoid overgrowth and cell-mediated immunological reaction *via* interleukin-1β (IL-1β) and tumor necrosis factor alpha (TNF-α), IL-6 and IL-8 and also medullasin [31]. The mediator medullasin activates the inflammatory response via modulating cytokines [31].

IL-13 induces the expression of TGF-β, which is a cytokine found in high concentrations in platelets, macrophages, neutrophils, and fibroblasts [32, 33]. It acts mainly on fibroblasts and endothelial cells and results in collagen and matrix synthesis [33]. This cytokine is maintained in the inactive form by binding non-covalently to a protein called Latency-Associated Protein (LAP) and stored within the cell as a homodimer [34]. Cathepsins and Matrix Metalloproteinases (MMPs) release the LAP from TGF- β and activate TGF-β [35]. IL-13 also increases the expression of MMP-2, MMP-9 and cathepsins [38]. Phenytoin enhances IL-13 secretion, thus TGF-β expression and produces its active form.

The occurrence of fibrosis requires both TGF-β and Connective Tissue Growth Factor (CTGF). In the gingival tissue, the effects of TGF-β are mainly *via* CTGF. However, in the gingival overgrowth tissue, the TGF-β is in a higher concentration in the initial period whereas the concentration of

CTGF remains high at a constant level [36]. This implicates that TGF-β induces the expression of CTGF through a cascade effect. CTGF is a known producer of fibrosis. It also increases the proliferation of fibroblasts due to its mitogenic, angiogenic and chemotactic activities [36].

The degradation of collagen occurs *via* two mechanisms. One is extracellularly, by collagenases and the second intracellularly following collagen phagocytosis [37]. MMPs are a family with 25 enzymes that are endopeptidases [38]. The action of MMPs depends on Calcium and Zinc; MMPs can be secreted or are membrane associated and vital in ECM metabolism [39]. As, MMPs are collagenases, stromelysins, and gelatinases, they are involved in tissue remodeling of ECM especially tissue degradation [38, 39]. MMP-1, also known as collagenase-1, degrades the fibrillar collagen through activating the inactive collagenase [39]. Any altered balance due to either activation or inhibition results in a change in the amount of ECM. Thus, inhibition of MMPs causes excessive accumulation of connective tissues in the ECM [40 - 42].

Natural MMP inhibitors exist in all animal tissues [43]. One of the main MMP inhibitor families is Tissue Inhibitors of Metalloproteinases (TIMPs) consisting of four types. MMP-1 mediated ECM remodeling, the degradation of ECM, is inhibited by TIMP-1, resulting in excessive accumulation of connective tissue in ECM. In addition, TIMP-1 has growth-promoting activity in several types of cells [44].

Phenytoin causes the inhibition of collagen degradation via MMPs/TIMP-1 [44, 45]. Phenytoin reduces intracellular folic acid and induces the production of mediators such as TGF-β and TNF-α [45]. The three main drug categories (phenytoin, cyclosporine and calcium channel blockers) causing drug induced gingival overgrowth have an inhibitory action on cation channels. Based on the available evidence, a unified theory has been proposed [4]. The antiepileptic action of phenytoin is mainly through the inhibition of sodium channels. However, phenytoin also inhibits the calcium channels, including in the gingival fibroblasts [46, 47]. Folic acid requirement depends on the type of tissue and is higher in some tissues including gingival tissues. This can result in local folate deficiency despite normal serum folate levels [4]. Cellular uptake of folic acid occurs through two mechanisms. The first is passive diffusion and the second cation dependent active transport [4, 48]. The cation dependent active cellular intake of folic acid is impaired by phenytoin [4]. This can result in a systemic and localized folate deficiency in the gingival tissue.

Decreased cellular folic acid leads to reduced expression of E-cadherin and SMAD (SMAD proteins are signal transducers and transcriptional modulators that mediate multiple signaling pathways) which reduces the expression of the AP-1 gene. Reduced AP-1 activates the TIMP-1 gene expression. The result is that phenytoin decreases the MMP-1 by increasing the expression of TIMP-1. As a result of this, collagen accumulates in ECM and causes gingival overgrowth [44, 49, 50].

Cathepsin degrades ECM components such as type 1 collagen, laminin and proteoglycans.

As phenytoin inhibits cathepsin, the result is the accumulation of ECM components [42, 51, 52].

Integrins are a large family of heterodimeric transmembrane receptors. Each heterodimer consists of α and β subunits. In mammals, there are 17α and 8β subunits that can form 40 different integrins through different combinations. The α1β1 integrin recognizes type IV collagen preferentially and the α2β1 integrin recognizes type 1 collagen preferentially [53]. Studies have indicated that α2β1 integrins serve as specific receptors of type I collagen in fibroblasts. For collagen phagocytosis, collagen should adhere to the fibroblast as the first step. It has been also shown that α2 integrin plays a critical role in the phagocytic regulation of collagen internalization by adhering to collagen [53]. Phenytoin reduces the collagen internalization, therefore causing degradation either by reducing the affinity of integrins to collagens or reducing the expression of integrins. A proposed mechanism for the reduced expression of integrins is diminished intracellular calcium due to the calcium channel antagonist effect of phenytoin. Hence, collagen accumulation in the ECM will result in gingival overgrowth [28].

Another mechanism through which phenytoin induces gingival overgrowth is by the conversion of androgens to their active metabolites. Studies have shown that fibroblasts of the gingiva have the ability to metabolize testosterone to its active metabolite 5α-dihydrotestosterone, enhanced by the addition of phenytoin to the cultured fibroblasts [54]. ECM synthesis could be enhanced by the stimulatory effect of phenytoin on the type 2 isoenzyme of 5α-reductase activity. This action takes place in either a ligand-dependent manner through the stimulation of their own receptors, or a ligand-independent manner, through the direct stimulation of the androgen receptor. Type 2 reductase of 5α-reductase, *via* the production of 5α-dihydrotestosterone, has an anabolic role in gingiva by activating the fibroblast cells to produce more collagen fibers or decrease collagenase activity [54]. Some authors have suggested that a trigger of alkaline phosphatase may mediate some of the matrix stimulatory actions of androgen metabolites [55]. Others have mentioned the role of oestrogens to increase the local level of dihydrotestosterone and thereby stimulating collagen formation. Oestrogen enhances the incorporation of proline in collagen molecules being synthesized in the gingival fibroblasts [56].

Phenytoin acts on macrophages, enhancing the production of IL-1β, which enhances the expression of Cyclooxygenase 2 (COX-2) through the transcription factor (nuclear factor-kappaB [NF-κB]. COX-2 is the main enzyme in the production of Prostaglandins (PGs) from arachidonic acid. One such important prostaglandin is PGE2 [30]. Transcription of TGF-β and its receptors are enhanced by PGE-2 [57]. EP-3 receptors are found in gingival fibroblasts but not in lung or kidney fibroblasts. PGE-2 acts on EP-3 receptors in gingival fibroblasts and enhances the TGF-β1 stimulation of JNK -MAP kinase pathway of CTGF expression [30].

Platelet Derived Growth Factor (PDGF), produced by platelets, macrophages, endothelial cells, and fibroblasts, is believed to enhance mitogenic activity and chemotaxis [58]. Phenytoin is also known to increase the production of PDGF. PDGF activates the cytosolic phospholipase A2 enzyme which releases arachidonic acid from the cell membrane by increasing

intracellular calcium. Apart from the indirect effect of PDGF, there is a direct effect by increasing the expression of COX-2 which has been proven in some studies [59, 60].

Epithelial Mesenchymal Transition (EMT) is a biological process of acquisition of the mesenchymal phenotype by the epithelial cells where it acquires an increased migratory capacity, invasiveness and importantly inhibition to apoptosis and enhanced ECM production. Normally, a polarized epithelial cell interacts with the basement membrane *via* its basal surface [61 - 63]. In EMT, there is a degradation of the basement membrane at the rete ridges and transformed epithelial cells migrate to the connective tissue. EMT is involved in several processes such as embryonic development, cancer progression, and epithelial injury [64]. The process of EMT involves the loss of the polarity of epithelial cells, cell-cell and cell matrix adhesion, remodeling and rearrangement to gain the features of mesenchymal cells [64].

E-cadherin is important in epithelial cell contact which is essential for the barrier function of epithelial tissue [65, 66]. In EMT, there is a reduction in the levels of E-cadherin expression which results in the loss of integrity and barrier function of the epithelial cells [66]. In EMT, a specific marker for fibroblast, Fibroblast Specific Protein-1 (FSP-1) and also fibronectin, and an alternatively spliced form of fibronectin (ED-A isoform), 19 are secreted and found in elevated levels [66 - 68].

Transforming Growth Factor (TGF-β) down regulates E-cadherin and potently stimulates the epithelial mesenchymal transition and at the same time, TGF-β increases the expression of MMP-9 and MMP-2 which degrade type IV collagen in the basement membrane and allow migration of epithelial cells and interact with connective tissue [69 - 71]. Some types of integrins activate the latent TGF-β and can promote EMT.

Forkhead box transcription factors (FOXO) proteins belong to a Forkhead family of transcription factors. It is involved in the activation or inhibition of many genes related to important cellular functions [59]. Importantly, it reduces anabolic metabolism, increases apoptosis and arrests the cell cycle. FOXO-1 enhances the production of TGF-β contributing to gingival overgrowth. Phenytoin is known to inhibit FOXO-1 [72, 73].

A recent study has revealed that Transient Receptor Potential Ankyrin (TRPA1) channels have an important role to play in the pathophysiologic mechanism of phenytoin-induced GE. The calcium-permeable ion channels TRPA1 [74], Transient receptor potential channels, of the vanilloid subtype (TRPV1), and its capsaicin-insensitive isoform TRPV1b are expressed in Human Gingival Fibroblasts (HGFs), in which phenytoin increase the intracellular calcium levels by acting on the mentioned ion channels [72]. Further, phenytoin did not augment the proliferative rate of HGFs whereas it induced extracellular matrix accumulation of collagen [72].

The role of phenytoin in death receptor-induced apoptosis of gingival fibroblasts has been explored in a laboratory study suggesting that phenytoin treatment decreases the proportion of apoptotic cells in gingival fibroblasts compared to a serum-free control culture. This is in response to the upregulation of cellular FLICE-Like Inhibitory Protein (c-FLIP), the cellular inhibitor of apoptosis 2 (cIAP2) and downregulation of Fas-Associated Protein with Death Domain (FADD), caspase-3, caspase-8, caspase-9 and TNF Receptor Associated Factor 2(TRAF2) by the effect of phenytoin on Receptor-Interacting serine/threonine-Protein Kinase 1(RIPK1) activity and (B-cell lymphoma 2) Bcl-2 activity [75].

3. SUMMARY FINDING(S) FROM THE STUDY

Although several mechanisms, both at a cellular and molecular level, have been proposed for phenytoin induced gingival overgrowth, there is a lack of understanding in these mechanisms of phenytoin induced gingival overgrowth. Hence, there is no treatment or prevention for the management of this condition. This prompts the necessity of future research in this field, particularly at a molecular level.

CONCLUSION

Phenytoin induced gingival overgrowth is a side effect with multifactorial etiology. Several mechanisms have been proposed addressing the pathophysiological mechanism of phenytoin induced gingival overgrowth both at a cellular and molecular level. Evidence suggests that the inflammatory changes in the gingival tissues orchestrate the interaction between phenytoin and fibroblasts particularly resulting in an increase in the ECM content. However, the mechanism of the production of inflammatory mediators is not fully understood. This, together with the high prevalence of phenytoin induced gingival overgrowth, warrants further research in this area in order to develop treatment and preventive strategies for the management of this condition.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest financial or otherwise.

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REFERENCES

[1] Gittaboyina S, Mana TK, Koduganti RR, Reddy PV. Amlodipine induced gingival enlargement. J Oral Res Rev 2016; 8(1): 23. [http://dx.doi.org/10.4103/2249-4987.182486]

[2] Newman MG, Takei HH, Klokkevold PR, Carranza FA. Carranza's Clinical Periodontology. 11th ed. St. Louis, MO: Elsevier Saunders 2012; pp. 118-30.

[3] Ahmed R, Sharma A, Halawa A. Post-transplant gingival hyperplasia: A brief review. J Renal Transplant Sci 2019; 2(2): 85-90.

[4] Brown RS, Arany PR. Mechanism of drug-induced gingival overgrowth revisited: A unifying hypothesis. Oral Dis 2015; 21(1): e51-61. [http://dx.doi.org/10.1111/odi.12264] [PMID: 24893951]

[5] Al Sharrad A, Said KN, Farook FF, *et al.* Awareness of the relationship between systemic and periodontal diseases among physicians and dentists in Saudi Arabia and Kuwait: Cross-sectional Study. Open Dent J 2019; 13: 288-95. [http://dx.doi.org/10.2174/1874210601913010288]

[6] Dongari A, McDonnell HT, Langlais RP. Drug-induced gingival overgrowth. Oral Surg Oral Med Oral Pathol 1993; 76(4): 543-8. [http://dx.doi.org/10.1016/0030-4220(93)90027-2] [PMID: 8233439]

[7] Beaumont J, Chesterman J, Kellett M, Durey K. Gingival overgrowth: Part 1: Aetiology and clinical diagnosis. Br Dent J 2017; 222(2): 85-91. [http://dx.doi.org/10.1038/sj.bdj.2017.71] [PMID: 28127024]

[8] Kulkarni AV, Kini R, Rao PK, Bhandarkar GP, Kashyap RR. Drug induced gingival enlargement: Dentist's dilemma. Cukurova Med J 2018; 43(3): 722-5. [http://dx.doi.org/10.17826/cumj.397485]

[9] Nishikawa S, Nagata T, Morisaki I, Oka T, Ishida H. Pathogenesis of drug-induced gingival overgrowth. A review of studies in the rat model. J Periodontol 1996; 67(5): 463-71. [http://dx.doi.org/10.1902/jop.1996.67.5.463] [PMID: 8724703]

[10] Murakami S, Mealey BL, Mariotti A, Chapple ILC. Dental plaque-induced gingival conditions. J Clin Periodontol 2018; 45(Suppl. 20): S17-27. [http://dx.doi.org/10.1111/jcpe.12937] [PMID: 29926503]

[11] Ponnaiyan D, Jegadeesan V, Cyclosporine A. Cyclosporine A: Novel concepts in its role in drug-induced gingival overgrowth. Dent Res J (Isfahan) 2015; 12(6): 499-506. [http://dx.doi.org/10.4103/1735-3327.170546] [PMID: 26759584]

[12] Nagata T, Ninomiya M, Mihara C, Kido J, Nishikawa S, Kataoka M. Etiology of drug-induced gingival overgrowth. Curr Issu Periodontics 2016; 7: 37-44.

[13] Grusovin MG. The treatment of periodontal diseases in elderly patients.Oral rehabilitation for compromised and elderly patients. Cham: Springer 2019; pp. 29-47. [http://dx.doi.org/10.1007/978-3-319-76129-9_3]

[14] Fabiana CM, Frederick SR, Xavier M. Side Effects of phenytoin in the oral cavity: A review. J Oral Health Dent Sci 2018; 2: 104.

[15] Doufexi A, Mina M, Ioannidou E. Gingival overgrowth in children: Epidemiology, pathogenesis, and complications. A literature review. J Periodontol 2005; 76(1): 3-10. [http://dx.doi.org/10.1902/jop.2005.76.1.3] [PMID: 15830631]

[16] Suneja B, Chopra S, Thomas AM, Pandian J. A clinical evaluation of gingival overgrowth in children on antiepileptic drug therapy. J Clin Diagn Res 2016; 10(1): ZC32-6. [http://dx.doi.org/10.7860/JCDR/2016/16443.7069] [PMID: 26894172]

[17] Samudrala P, Chava VK, Chandana TS, Suresh R. Drug-induced gingival overgrowth: A critical insight into case reports from over two decades. J Indian Soc Periodontol 2016; 20(5): 496-502. [http://dx.doi.org/10.4103/jisp.jisp_265_15] [PMID: 29242684]

[18] Dongari-Bagtzoglou A. Research, science and therapy committee, american academy of periodontology. Drug-associated gingival enlargement. J Periodontol 2004; 75(10): 1424-31. [http://dx.doi.org/10.1902/jop.2004.75.10.1424] [PMID: 15562922]

[19] Saleem S, Verma S, Yousuf I, Wani MA, Asmi R. Diphenylhydantoin induced severe gingival hyperplasia. JMS SKIMS 2017; 20(1): 44-6. [http://dx.doi.org/10.33883/jms.v20i1.311]

[20] Taleghani F, Sheikhnejad H, Shidfar S, Hamzelouie E, Zohri Z. Drug induced gingival enlargement. J Chem Pharmaceutic Res 2016; 8(1): 439-46.

[21] Barrientos S, Stojadinovic O, Golinko MS, Brem H, Tomic-Canic M. Growth factors and cytokines in wound healing. Wound Repair Regen 2008; 16(5): 585-601. [http://dx.doi.org/10.1111/j.1524-475X.2008.00410.x] [PMID: 19128254]

[22] Angelopoulos AP, Goaz PW. Incidence of diphenylhydantoin gingival hyperplasia. Oral Surg Oral Med Oral Pathol 1972; 34(6): 898-906. [http://dx.doi.org/10.1016/0030-4220(72)90228-9] [PMID: 4509004]

[23] Farook FF, Said KN. A review of the effectiveness of antiseptic mouth rinses for oral health. J Oral Hyg Health 2018; 6: 246. [http://dx.doi.org/10.4172/2332-0702.1000246]

[24] Corrêa JD, Queiroz-Junior CM, Costa JE, Teixeira AL, Silva TA. Phenytoin-induced gingival overgrowth: A review of the molecular, immune, and inflammatory features. ISRN Dent 2011; 2011 [http://dx.doi.org/10.5402/2011/497850]

[25] Bigger JT Jr, Schmidt DH, Kutt H. Relationship between the plasma level of diphenylhydantoin sodium and its cardiac antiarrhythmic effects. Circulation 1968; 38(2): 363-74. [http://dx.doi.org/10.1161/01.CIR.38.2.363] [PMID: 5666850]

[26] Guldiken B, Rémi J, Noachtar S. Cardiovascular adverse effects of phenytoin. J Neurol 2016; 263(5): 861-70. [http://dx.doi.org/10.1007/s00415-015-7967-1] [PMID: 26645393]

[27] Mavrogiannis M, Ellis JS, Thomason JM, Seymour RA. The management of drug-induced gingival overgrowth. J Clin Periodontol 2006; 33(6): 434-9. [http://dx.doi.org/10.1111/j.1600-051X.2006.00930.x] [PMID: 16677333]

[28] Karimzadeh I, Namazi S, Borhani-Haghighi A, Khosropanah H. Phenytoin-induced gingival over growth: A review. Soc Pharmacy J 2015; 1(1)

[29] Trackman PC, Kantarci A. Molecular and clinical aspects of drug-induced gingival overgrowth. J Dent Res 2015; 94(4): 540-6. [http://dx.doi.org/10.1177/0022034515571265] [PMID: 25680368]

[30] Man Y, Hart VJ, Ring CJ, Sanjar S, West MR. Loss of epithelial integrity resulting from E-cadherin dysfunction predisposes airway epithelial cells to adenoviral infection. Am J Respir Cell Mol Biol 2000; 23(5): 610-7. [http://dx.doi.org/10.1165/ajrcmb.23.5.4046] [PMID: 11062139]

[31] Morand DN, Davideau JL, Clauss F, Jessel N, Tenenbaum H, Huck O. Cytokines during periodontal wound healing: Potential application for new therapeutic approach. Oral Dis 2017; 23(3): 300-11. [http://dx.doi.org/10.1111/odi.12469] [PMID: 26945691]

[32] Seymour RA, Ellis JS, Thomason JM. Risk factors for drug-induced gingival overgrowth. J Clin Periodontol 2000; 27(4): 217-23. [http://dx.doi.org/10.1034/j.1600-051x.2000.027004217.x] [PMID: 10783833]

[33] Nickel J, Ten Dijke P, Mueller TD. TGF-β family co-receptor function and signaling. Acta Biochim Biophys Sin (Shanghai) 2018; 50(1): 12-36. [http://dx.doi.org/10.1093/abbs/gmx126] [PMID: 29293886]

[34] Mohan V, Talmi-Frank D, Arkadash V, Papo N, Sagi I. Matrix metalloproteinase protein inhibitors: Highlighting a new beginning for metalloproteinases in medicine. Metalloprot Med 2016; 3: 31. [http://dx.doi.org/10.2147/MNM.S65143]

[35] Uzel MI, Kantarci A, Hong HH, *et al.* Connective tissue growth factor in drug-induced gingival overgrowth. J Periodontol 2001; 72(7): 921-31. [http://dx.doi.org/10.1902/jop.2001.72.7.921] [PMID: 11495141]

[36] Gonzalez AC, Costa TF, Andrade ZA, Medrado AR. Wound healing - A literature review. An Bras Dermatol 2016; 91(5): 614-20. [http://dx.doi.org/10.1590/abd1806-4841.20164741] [PMID: 27828635]

[37] Jabłońska-Trypuć A, Matejczyk M, Rosochacki S. Matrix metalloproteinases (MMPs), the main extracellular matrix (ECM) enzymes in collagen degradation, as a target for anticancer drugs. J Enzyme Inhibit Med Chem 2016; 31(sup1): 177-83.

[38] Mittal R, Patel AP, Debs LH, *et al.* Intricate functions of matrix metalloproteinases in physiological and pathological conditions. J Cell Physiol 2016; 231(12): 2599-621. [http://dx.doi.org/10.1002/jcp.25430] [PMID: 27187048]

[39] Malemud CJ. Matrix metalloproteinases (MMPs) in health and disease: An overview. Front Biosci 2006; 11: 1696-701. [http://dx.doi.org/10.2741/1915] [PMID: 16368548]

[40] Maita E, Sato M, Yamaki K. Effect of tranilast on matrix metalloproteinase-1 secretion from human gingival fibroblasts *in vitro*. J Periodontol 2004; 75(8): 1054-60. [http://dx.doi.org/10.1902/jop.2004.75.8.1054] [PMID: 15455731]

[41] Kim SS, Nikoloudaki G, Darling M, Rieder MJ, Hamilton DW. Phenytoin activates Smad3 phosphorylation and periostin expression in drug-induced gingival enlargement. Histol Histopathol 2018; 33(12): 1287-98. [PMID: 29916554]

[42] Iman K, Soha N, Afshin BH, *et al.* Phenytoin-induced gingival over growth: A review soc. Pharm J 2015; 1(1)e827

[43] Wynn TA. Cellular and molecular mechanisms of fibrosis. J Pathol 2008; 214(2): 199-210. [http://dx.doi.org/10.1002/path.2277] [PMID: 18161745]

[44] Kato T, Okahashi N, Kawai S, *et al.* Impaired degradation of matrix collagen in human gingival fibroblasts by the antiepileptic drug phenytoin. J Periodontol 2005; 76(6): 941-50. [http://dx.doi.org/10.1902/jop.2005.76.6.941] [PMID: 15948689]

[45] Fugii A, Kobayashi S. Nifedipine inhibits calcium uptake of nifedipine-sensitive gingival fibroblast. J Dent Res 1990; 67: 332.

[46] Modéer T, Brunius G, Mendez C, Juntti-Berggren L, Berggren PO.

Influence of phenytoin on cytoplasmic free Ca^{2+} level in human gingival fibroblasts. Scand J Dent Res 1991; 99(4): 310-5. [http://dx.doi.org/10.1111/j.1600-0722.1991.tb01033.x] [PMID: 1771377]

[47] Ariel M, Eilam Y, Jablonska M, *et al.* On the mechanism of folate transport in isolated intestinal epithelial cells. J Pharmacol Exp Ther 1982; 223: 224-46. [PMID: 7120120]

[48] Crott JW, Liu Z, Keyes MK, *et al.* Moderate folate depletion modulates the expression of selected genes involved in cell cycle, intracellular signaling and folate uptake in human colonic epithelial cell lines. J Nutr Biochem 2008; 19(5): 328-35. [http://dx.doi.org/10.1016/j.jnutbio.2007.05.003] [PMID: 17681772]

[49] Ganesh PR. Immunoexpression of interleukin-6 in drug-induced gingival overgrowth patients. Contemp Clin Dent 2016; 7(2): 140-5. [http://dx.doi.org/10.4103/0976-237X.183048] [PMID: 27307657]

[50] Vizovišek M, Fonović M, Turk B. Cysteine cathepsins in extracellular matrix remodeling: Extracellular matrix degradation and beyond. Matrix Biol 2019; 75-76: 141-59. [PMID: 29409929]

[51] Yamada H, Nishimura F, Naruishi K, *et al.* Phenytoin and cyclosporin A suppress the expression of MMP-1, TIMP-1, and cathepsin L, but not cathepsin B in cultured gingival fibroblasts. J Periodontol 2000; 71(6): 955-60. [http://dx.doi.org/10.1902/jop.2000.71.6.955] [PMID: 10914799]

[52] Kataoka M, Kido J, Shinohara Y, Nagata T. Drug-induced gingival overgrowth-A review. Biol Pharm Bull 2005; 28(10): 1817-21. [http://dx.doi.org/10.1248/bpb.28.1817] [PMID: 16204928]

[53] Soory M, Suchak A. The effects of human mast-cell products and of phenytoin on androgen 5alpha-reductase expression in human gingival fibroblasts. Arch Oral Biol 2001; 46(9): 847-55. [http://dx.doi.org/10.1016/S0003-9969(01)00037-1] [PMID: 11420057]

[54] Soory M, Suchak A. Effects of alkaline phosphatase and its inhibitor levamisole on the modulation of androgen metabolism by nicotine and minocycline in human gingival and oral periosteal fibroblasts. Arch Oral Biol 2003; 48(1): 69-76. [http://dx.doi.org/10.1016/S0003-9969(02)00157-7] [PMID: 12615144]

[55] Patil MM, Sahoo J, Kamalanathan S, Pillai V. Phenytoin induced osteopathy-Too common to be neglected. J Clin Diagn Res 2015; 9(11): OD11-2. [JCDR]. [http://dx.doi.org/10.7860/JCDR/2015/15224.6820] [PMID: 26674262]

[56] Brunius G, Yucel-Lindberg T, Shinoda K, Modéer T. Effect of phenytoin on interleukin-1 beta production in human gingival fibroblasts challenged to tumor necrosis factor alpha *in vitro*. Eur J Oral Sci 1996; 104(1): 27-33. [http://dx.doi.org/10.1111/j.1600-0722.1996.tb00042.x] [PMID: 8653494]

[57] Kuru L, Yilmaz S, Kuru B, Köse KN, Noyan U. Expression of growth factors in the gingival crevice fluid of patients with phenytoin-induced gingival enlargement. Arch Oral Biol 2004; 49(11): 945-50. [http://dx.doi.org/10.1016/j.archoralbio.2004.04.010] [PMID: 15353252]

[58] Finkenzeller G, Totzke F, Fitzke E, Marmé D, Dieter P. Over-expression of protein kinase C-alpha enhances platelet-derived growth factor- and phorbol ester- but not calcium ionophore-induced formation of prostaglandins in NIH 3T3 fibroblasts. FEBS Lett 1993; 321(1): 11-4. [http://dx.doi.org/10.1016/0014-5793(93)80610-7] [PMID: 8467904]

[59] Manimegalai AG, Rao SH, Ravindran D. Fibronectin in periodontal health and disease. J Orofac Sci 2016; 8(1): 12. [http://dx.doi.org/10.4103/0975-8844.181918]

[60] Smith PC. Role of myofibroblasts in normal and pathological periodontal wound healing. Oral Dis 2018; 24(1-2): 26-9. [http://dx.doi.org/10.1111/odi.12773] [PMID: 29480623]

[61] Kalluri R, Neilson EG. Epithelial-mesenchymal transition and its implications for fibrosis. J Clin Invest 2003; 112(12): 1776-84. [http://dx.doi.org/10.1172/JCI200320530] [PMID: 14679171]

[62] Kalluri R, Weinberg RA. The basics of epithelial-mesenchymal transition. J Clin Invest 2009; 119(6): 1420-8. [http://dx.doi.org/10.1172/JCI39104] [PMID: 19487818]

[63] Zavadil J, Böttinger EP. TGF-beta and epithelial-to-mesenchymal transitions. Oncogene 2005; 24(37): 5764-74. [http://dx.doi.org/10.1038/sj.onc.1208927] [PMID: 16123809]

[64] Takeuchi R, Matsumoto H, Arikawa K, *et al.* Phenytoin-induced gingival overgrowth caused by death receptor pathway malfunction. Oral Dis 2017; 23(5): 653-9. [http://dx.doi.org/10.1111/odi.12651] [PMID: 28160766]

[65] Sume SS, Kantarci A, Lee A, Hasturk H, Trackman PC. Epithelial to mesenchymal transition in gingival overgrowth. Am J Pathol 2010; 177(1): 208-18. [http://dx.doi.org/10.2353/ajpath.2010.090952] [PMID: 20489142]

[66] Iwano M, Plieth D, Danoff TM, Xue C, Okada H, Neilson EG. Evidence that fibroblasts derive from epithelium during tissue fibrosis. J Clin Invest 2002; 110(3): 341-50. [http://dx.doi.org/10.1172/JCI0215518] [PMID: 12163453]

[67] Maldve RE, Kim Y, Muga SJ, Fischer SM. Prostaglandin E(2) regulation of cyclooxygenase expression in keratinocytes is mediated *via* cyclic nucleotide-linked prostaglandin receptors. J Lipid Res 2000; 41(6): 873-81. [PMID: 10828079]

[68] Strutz F, Zeisberg M, Ziyadeh FN, *et al.* Role of basic fibroblast growth factor-2 in epithelial-mesenchymal transformation. Kidney Int 2002; 61(5): 1714-28. [http://dx.doi.org/10.1046/j.1523-1755.2002.00333.x] [PMID: 11967021]

[69] Li Y, Yang J, Dai C, Wu C, Liu Y. Role for integrin-linked kinase in mediating tubular epithelial to mesenchymal transition and renal interstitial fibrogenesis. J Clin Invest 2003; 112(4): 503-16. [http://dx.doi.org/10.1172/JCI200317913] [PMID: 12925691]

[70] Kantarci A, Augustin P, Firatli E, *et al.* Apoptosis in gingival overgrowth tissues. J Dent Res 2007; 86(9): 888-92. [http://dx.doi.org/10.1177/154405910708600916] [PMID: 17720861]

[71] Sharma PK, Misra AK, Chugh A, Chugh VK, Gonnade N, Singh S. Gingival hyperplasia: Should drug interaction be blamed for? Indian J Pharmacol 2017; 49(3): 257-9. [http://dx.doi.org/10.4103/ijp.IJP_57_17] [PMID: 29033487]

[72] López-González MJ, Luis E, Fajardo O, *et al.* TRPA1 channels mediate human gingival fibroblast response to phenytoin. J Dent Res 2017; 96(7): 832-9. [http://dx.doi.org/10.1177/0022034517695518] [PMID: 28571526]

[73] Ramírez-Rámiz A, Brunet-LLobet L, Lahor-Soler E, Miranda-Rius J. On the cellular and molecular mechanisms of drug-induced gingival overgrowth. Open Dent J 2017; 11: 420-35. [http://dx.doi.org/10.2174/1874210601711010420] [PMID: 28868093]

[74] Viana F. TRPA1 channels: Molecular sentinels of cellular stress and tissue damage. J Physiol 2016; 594(15): 4151-69. [http://dx.doi.org/10.1113/JP270935] [PMID: 27079970]

[75] Kasai H, Allen JT, Mason RM, Kamimura T, Zhang Z. TGF-beta1 induces human alveolar epithelial to mesenchymal cell transition (EMT). Respir Res 2005; 6: 56. [http://dx.doi.org/10.1186/1465-9921-6-56] [PMID: 15946381]