

[MINI REVIEW]

Effect of psychological stress on aging and its implication on the oral cavity : A mini-review

Dedy ARIWANS¹, Durga PAUDEL², Tetsuro MORIKAWA¹, Jun SATO¹, Koki YOSHIDA¹, Osamu UEHARA³,
Hirofumi MATSUOKA³, Shuhei TAKAHASHI¹, Hiroko MIURA³, Yoshihiro ABIKO¹

¹Division of Oral Medicine and Pathology, School of Dentistry, Health Sciences University of Hokkaido, Japan

²Advanced Research Promotion Center, Health Sciences University of Hokkaido, Japan

³Division of Molecular Epidemiology and Disease Control, School of Dentistry, Health Sciences University of Hokkaido, Japan

Key words : psychological stress, aging, DNA damage, telomere, epigenetics

Abstract

Stress is any influence of the internal or external environment on a living being that disrupts its homeostasis. The relationship between chronic psychological stress and mental disorders and some age-related diseases has been demonstrated in previous studies. Chronic psychological stress may cause accelerated aging through multiple mechanisms such as DNA damage, systemic inflammation, telomere shortening, and

mitochondrial dysfunction. However, comprehensive knowledge of how psychological stress may contribute to accelerated aging is limited. Here, we summarize the findings that relate psychological stress to aging, explore possible mechanisms of how psychological stress is involved in the process and discuss its implication on oral tissues.

Introduction

Stress is any influence of the internal or external environment on a living being that disrupts its homeostasis. The body tries to adapt to stress through various stress response systems. However, when the amount of stress experienced by a person is beyond their adaptive capability, it could endanger physical and mental conditions (Kupriyanov & Zhdanov, 2014). Chronic psychological stress may lead to mental disorders such as depression, maladjustment or maladaptation, and post-traumatic stress disorder. Psychological stress can also increase the risk of cardiovascular, autoimmune, and neurodegenerative diseases as well as cancer (Dube et al., 2009).

Aging is progressive physiological changes resulting in a decline of biological functions. Aging is characterized by the development of a mild pro-inflammatory state commonly termed as inflammaging (Bektas et al., 2018). The prolonged inflammation may lead to pathological conditions (Bektas et al., 2018). Although aging is a physiologic process, environmental factors such as nutrition, radiation, and chronic sys-

temic diseases may accelerate the aging process (Addor, 2018). In addition, psychological stresses may influence accelerated aging (Yegorov et al., 2020). The physiological response to stress brings the cascade of stress hormones and inflammatory cytokines (Yegorov et al., 2020). The molecular changes in chronic psychological stress may cause accelerated aging through multiple mechanisms such as DNA damage, systemic inflammation, telomere shortening, and mitochondrial dysfunction (Yegorov et al., 2020). Although various studies have associated psychological stress with aging, comprehensive knowledge is still lacking. The objective of this review is to summarize the findings that relate psychological stress to aging, explore possible mechanisms of how psychological stress is involved in the process and discuss its implication on oral tissues.

Psychological Stress and body response

The body's response to stress generally involves two pathways : Sympatho-Adrenomedullary Pathway (SAM) and the Hypothalamic-Pituitary-Adrenal (HPA) pathway (Sharpley, 2009). The first stress response pathway is the sympatho-

adrenomedullary (SAM) axis. It acts via the sympathetic nervous system (SNS) and the adrenal medulla to respond very quickly to stressors. Physical stressors produce afferent signals from organs to the Central Nervous System (CNS) and cause an immediate response via the autonomic nervous system (ANS) reflexive processes (Bartolomucci & Leopardi, 2009). Adrenaline leads to the arousal of the sympathetic nervous system and reduced activity in the parasympathetic nervous system. Adrenaline creates changes in the body such as increased sweating, increased pulse, and blood pressure (Godoy et al., 2018). The second stress response pathway is the hypothalamic–pituitary–adrenal (HPA) axis. In the HPA axis stress response regulation, the hypothalamus secretes multiple hormones, including the corticotropin–releasing hormone (CRH) and stimulates the pituitary gland to secrete the Adrenocorticotrophic hormone (ACTH) into the bloodstream (O'Connor et al., 2000). ACTH acts on adrenal glands and stimulates the adrenal cortex to secrete glucocorticoids including cortisol, which acts upon target cells via intracellular glucocorticoid receptors. Cortisol binds to cytosolic glucocorticoid receptor proteins present in most tissues, enters the cell nucleus, and alters the expression of specific genes and mRNAs (Epel & Lithgow, 2014). Cortisol can increase heart rate, vasoconstriction, and blood pressure, the release of stored lipids and amino acids from fatty tissue and helps the body defend itself against infectious agents by stabilizing the membranes of lysosomes (Epel & Lithgow, 2014).

Mechanisms Stress Influences Aging in The Body

A physiological stress response to psychosocial stress and the associated cascade of stress hormones may accelerate biological aging through multiple pathways. Some possible mechanisms by which psychological stress may influence the aging process in the body are summarized in Table.1. Various mechanisms such as DNA damage including telomere length, telomere activity, and epigenetic alteration, alteration in immune cells, and morphological and functional alterations in the brain have been identified as possible mechanisms involved in the process. These mechanisms are briefly discussed below.

3.1 DNA damage

DNA damage over time is a hallmark of the aging proc-

ess. DNA is damaged by various external factors such as diet, environment, radiation, temperature, and psychological stress, among others, and internal factors such as oxidative stress, advanced glycation end products, and spontaneous reactions, among others. DNA damage accumulation over time triggers the signaling pathways driving cells toward apoptosis or senescence. Various mechanisms such as reduced telomere length and activity, increased apoptosis, increased oxidative stress and epigenetic changes are involved in promoting aging by DNA damage (Maynard et al., 2015).

Psychological stress may contribute to aging by inducing DNA damage. Stress hormones, such as cortisol, nor–epinephrine, and epinephrine have been shown to induce DNA damage by altering the DNA repair capacity or by restricting the induction of apoptosis of cells with DNA lesions (Flint et al., 2007). Some human studies showed that stress hormones, cortisol, and nor–epinephrine can increase DNA damage and alter transcriptional regulation of the cell cycle (Flint et al., 2007). Basically, in psychological stress, DNA damage such as telomere length and epigenetic alteration has been identified to contribute to the aging (Flint et al., 2007).

3.1.1 Telomere Length

Chromosomal ends are capped by DNA–protein complexes known as telomeres, which promote chromosomal stability. These telomeres shorten with every cell division due to incomplete replication by the lagging strand of the replication fork. The telomere shortening contributes to the persistent DNA damage response (DDR). The DDR basically preserves the genome integrity by arresting cell cycle progression for the DNA repair process (Hewitt et al., 2012). The cell cycle arrest is regulated by pathways such as phosphorylation, acetylation, ubiquitylation, and SUMOylation. The DDR in the aging process causes the inability of tissues to further proliferate and form new cells (Hewitt et al., 2012). Also, the extracellular matrix–degrading enzymes and inflammatory cytokines are upregulated and this process contributes to the progressive decline in the biological function of the tissues (Hewitt et al., 2012). Telomeres shortening in psychological stress have been shown in human studies. Telomere length was significantly shorter in individuals with mood disorders, indicating accelerated aging of up to ten years (Simon et al., 2006). Psychological stress was associated with increased oxidative stress, reduced telomerase activity, and shorter telomere lengths in peripheral blood

Table 1. Studies showing the possible mechanism of psychological stress contributing to aging

A. Telomere length	Reference
Women with the highest levels of perceived stress had short telomeres on average by the equivalent of at least one decade of additional aging compared to low-stress women.	Epel, et al 2004
Live-cell imaging experiments revealed all persistent DNA damage foci in stress induced senescence were associated with telomeres ; An age-dependent increase in frequencies of telomere-associated foci in the gut and liver of mice, occurring irrespectively of telomere length.	Hewitt, et al 2012
Childhood maltreatment had significantly shorter telomeres than those who did not report a history of maltreatment ; Analysis of subscales showed that both physical neglect and emotional neglect were significantly linked to telomere length.	Tyrka, et al 2009
Telomere length was significantly shorter in individual with mood disorders, representing as much as 10 years of accelerated aging.	Simon, et al 2006
B. Immune cells	
The exposure of cortisol, a stress hormone to human T lymphocytes was associated with a significant reduction in telomerase activity. The effect was observed in both CD4 and CD8 T lymphocytes and was associated with reduced transcription of hTERT, the telomerase catalytic component.	Choi, 2008
Life trauma and chronic stress was related to a lower percentage of CD4+ naïve cells ; Stressful life events, high lifetime discrimination, and chronic stress were associated with a higher percentage of terminally differentiated CD8+ cells.	Klopach, et al 2022
C. Cytokines	
Stressful job such as in caregivers, the average rate of increase in interleukin-6 (IL-6) was about four times as large as that of non-caregivers.	Glaser, et al 2003
Omega-3 supplementation altered telomerase and IL-10 stress reactivity ; Omega-3 also reduced overall cortisol and IL-6 throughout the stressor compared to the placebo group.	Madison, et al 2021
D. Morphological & functional alteration in the brain	
Tg-APPswe/PS1dE9 mice that were restrained had significantly increased A β (1-42) levels and plaque deposition in the brain ; The 2-h/16-day stress increased oxidative stress and induced mitochondrial dysfunction in the brain.	Seo, et al 2011
After correcting for antidepressant use, brain predicted age difference was significantly higher in major depressive disorder compared with controls.	Han, et al 2021
E. Epigenetic alteration	
The age/stress-related epigenetic signature enhanced FKBP5 response to NF- κ B through a positive feedback loop highlighting relation between aging, stress and inflammation.	Zannas, et al 2019
A high number (n =85) of epigenetic clock CpG sites were located within glucocorticoid response elements. Cumulative lifetime stress might accelerate epigenetic aging.	Zannas, et al 2015
Development of post-traumatic stress disorder symptoms was negatively associated with the telomere lengthening. Trauma significantly accelerated epigenetic ageing.	Boks, et al 2015
Cumulative stress was associated with accelerated aging and stress-related physiologic measures of adrenal sensitivity (Cortisol/ACTH ratio)	Harvanek, et al 2021

mononuclear cells (Epel et al., 2004). The telomeres of women who were under high levels of perceived stress were shorter by at least one decade compared to women who were under low levels of perceived stress (Epel et al., 2004). The elevated level of stress hormones such as catecholamines and cortisol were associated with lower telomerase activity in leukocytes (Tyrka et al., 2010). Individuals with childhood stress due to physical and emotional neglect had significantly shorter telomeres than those without such history (Tyrka et al., 2010). An in vivo experiment also confirmed that up to half of the DNA damage foci in stress-induced senescence are located at telomeres irrespective of the telomerase activity (Hewitt et al., 2012). These findings suggest that telomeres may be shortened by psychological stress as well as aging.

3.1.2 Epigenetic alteration

Epigenetic alterations caused by environmental factors regulate gene expression without alteration in genetic sequence. Various mechanisms such as DNA methylation, acetylation, and histone modification are involved in epigenetic alterations (Gibney and Nolan, 2010). The aging process contributes to these epigenetic changes, mainly DNA methylation. Prediction of chronological age based on DNA methylation is commonly known as the “epigenetic clock”. (Harvanek et al., 2021).

Recent studies suggest that various types of psychological stressors may accelerate biological aging by altering the DNA methylation (Boks et al., 2015). Individuals with major depression, post-traumatic stress disorder, childhood adversity, and childhood abuse have accelerated aging following epigenetic modifications (Boks et al., 2015). The effect of these life stressors was observed as a high number of

methylated CpG sites located within the glucocorticoid response elements (Zannas et al., 2015). Some gene loci such as in FKBP5, a stress-responsive gene may synergize with aging to decrease DNA methylation at selected CpGs located near the transcription start site. This change in methylation of the FKBP5 gene may activate NF- κ B and promote inflammation (Zannas et al., 2019). These findings suggest that alterations of DNA methylation induced by psychological stress may be involved in the aging process.

3.2 Immune Cells

Immunological aging encompasses age-associated decline in the immune system (immunosenescence) and increases in inflammation (inflammaging) (Reed, 2019). The hallmarks of immunosenescence include changes in the adaptive immune system, mostly T cells (Reed, 2019). Decrease in naïve T cells and accumulation of memory T cells, mainly late differentiated senescent CD8+ T cells are observed with aging accompanied by shortened telomeres (Reed, 2019).

Several studies showed that psychological stress altered the immune system the same as it affected aging. Psychosocial stress such as life trauma, high lifetime discrimination, and chronic stress was identified as a contributor to accelerating immune aging by decreasing naïve and increasing terminally differentiated T cells (Klopach et al., 2022). The exposure of cortisol, a stress hormone to human T lymphocytes significantly reduced telomerase activity. The effects were observed in both CD4 and CD8 T lymphocytes, which led to reduced transcription of hTERT, the telomerase catalytic component (Choi et al., 2008). The alterations of immune cells affected by psychological stress may influence aging.

Cytokines produced through immune cells also associate psychological stress with aging. Interleukin (IL)-6 and other proinflammatory cytokines released from macrophages and T lymphocytes can be directly stimulated by stress, anxiety, and depression (Dentino et al., 1999). An observational study showed that the average rate of increase in interleukin-6 (IL-6) in caregivers with stressful work was about four times as large as that of non-caregivers (Kiecolt-Glaser et al., 2003). Omega-3, an effective agent for anti-aging was able to reduce overall cortisol and IL-6 level, which may provide data on the association among aging, stress, and inflammation. (Madison et al., 2021).

3.3 Morphological & function alteration in the brain

The brain undergoes morphological and functional alterations with aging. The medial posterior cingulate cortex mPCC-deactivations are known to be modulated by chronological aging, with more deactivations in the young than in the old (Oei et al., 2018). Age-related differences in cortical thickness were observed in the prefrontal cortex, central motor cortex, cingulate cortex, and bilateral lingual gyri. Amyloid beta deposition in the brain is also a characteristic feature of aging (Oei et al., 2018).

Psychological stress and other psychiatric disorders also show morphological and functional alterations in the brain similar to those observed with aging (Sheth et al., 2017 ; Carrier et al., 2021). Brain aging is more advanced in patients with major depressive disorder (MDD) (Han et al., 2021). Significant reduction in the thickness of the prefrontal cortex and cingulate cortex was associated with life event stress (Baldacara et al., 2017 ; Belleau et al., 2019). Chronic stress over a lifetime often led to poorer cognitive function (Scott et al., 2015). Animal studies showed that restraint stress aggravated amyloid beta deposition in the brain as the process of accelerated aging (Seo et al., 2011). Psychological stress may accelerate the aging process through morphological and functional alteration in the brain.

Psychological stress and aging of oral tissue

Psychological stress may affect the oral tissue and contribute to accelerated aging. Previous studies have highlighted the effect of psychological stress on the oral cavity including saliva, submandibular glands, and oral microbiota (Paudel et al., 2020 ; Paudel et al., 2022). Similar to aging, reduced periodontal tissue functions due to psychological stress have already been demonstrated (Spektor et al., 2020 ; Villalobos et al., 2022). Psychological stress may contribute to the accelerated aging of oral tissue by mechanisms discussed in previous sections (Spektor et al., 2020 ; Villalobos et al., 2022). Epigenetic alterations in the oral tissues have been shown by both psychological stress and aging. Psychological stresses could induce epigenetic alterations in saliva and buccal mucosa (Jiang S, et al. 2019). Epigenetic clocks based on samples from saliva or buccal mucosa have been shown to predict the biological age (Ambroa-Conde et al., 2022). Psychological stresses may induce other aging mechanisms including telomere shortening and altered immune cells in the oral tissues. However, studies are limited

to the direct link between psychological stress and aging in the oral tissues. Further studies are required to prove this hypothesis.

Conclusion

Psychological stress may contribute to accelerated aging in various tissues including oral tissues by various mechanisms such as DNA damage, alteration of immune cells, and various morphological and functional alterations in the brain.

Conflict of Interest

There is no conflict of interest associated with this study.

References

- Ambroa-Conde A, Giron-Santamaría L, Mosquera-Miguel A, Phillips C, Casares de Cal MA, Gomez-Tato A, Alvarez-Dios J, de la Puente M, Ruiz-Ramírez J, Lareu MV & Freire-Aradas A. Epigenetic age estimation in saliva and in buccal cells. *Forensic Sci Inter : Genetics* 61 : 1–10, 2022.
- Addor FAS. Beyond photoaging : additional factors involved in the process of skin aging. *Clin Cosmet Investig Dermatol* 11 : 437–443, 2018.
- Baldacara L, Araujo C, Assuncao I, Da Silva I, & Jackowski AP. Reduction of prefrontal thickness in military police officers with post-traumatic stress disorder. *Arch Clin Psychiatry* 44(4) : 94–98, 2017.
- Bartolomucci A & Leopardi R. Stress and Depression : Pre-clinical Research and Clinical Implications. *PLoS ONE* 4 (1) : 1–5, 2009.
- Bektas A, Schurman SH, Sen R & Ferucci L. Aging, inflammation and the environment. *Exp Gerontol* 105 : 10–18, 2008.
- Belleau EL, Treadway MT & Pizzagalli DA. The impact of stress and major depressive disorder on hippocampal and medial prefrontal cortex morphology. *Biol Psychiatry* 85 (6) : 443–453, 2019.
- Boks MP, Mierlo HC, Rutten BPF, Radstake TRDJ, Witte LD, Geuze E, Horvath S, Schalkwyk LC, Vinkers CH, Broen JCA & Vermetten E. Longitudinal changes of telomere length and epigenetic age related to traumatic stress and post-traumatic stress disorder. *Psychoneuroendocrinology* 51 : 506–512 ; 2015.
- Carrier M, Simoncicova E, St-Pierre MK, McKee C & Tremblay ME. Psychological stress as a risk factor for accelerated cellular aging and cognitive decline : the involvement of microglia–neuron crosstalk. *Front. Mol. Neurosci* 14(749737) : 1–17, 2021.
- Choi J, Fauchet SR & Effros RB. Reduced telomerase activity in human T lymphocytes exposed to cortisol. *Brain, Behavior and Immunity* 22(4) : 600–605, 2008.
- Dentino AN, Pieper CF, Rao MK, Currie MS, Harris T, Blazer DG, & Cohen Association of Interleukin–6 and other biologic variables with Depression in Older People Living in the Community. *Jour of The American Geriatrics Society* 47(1) : 6–11, 1999.
- Dube SR, Fairweather DL, Pearson WS, Felitti VJ, Anda RF, & Croft JB. Cumulative childhood stress and autoimmune diseases in adults. *Psychosomatic Medicine* 71(2) : 243–250, 2009.
- Epel ES, Blackburn EH, Lin J, Dhabhar FS, Adler NE, Morrow JD & Cawthon RM. Accelerated telomere shortening in response to life stress. *PNAS* 101(49) : 17312–17315, 2004.
- Epel ES & Lithgow GJ. Stress Biology and Aging Mechanisms : Toward Understanding the Deep Connection Between Adaptation to Stress and Longevity. *The Journals of Gerontology* 69(1) : S10–S16, 2014.
- Flint MS, Baum A, Chambers WH & Jenkins FJ. Induction of DNA damage, alteration of DNA repair, and transcriptional activation by stress hormones. *Psychoneuroendocrinology* 32(5) : 470–479, 2007.
- Godoy LD, Rossignoli MT, Pereira PD, Garcia-Cairasco N & Umeoka EHL. A Comprehensive Overview on Stress Neurobiology : Basic Concepts and Clinical Implications. *Front. Behav. Neurosci* 12(127) : 1–23, 2018.
- Han LKM, Penninx BWJH, Marquand AF, Cole JH & Schmaal L. Brain aging in major depressive disorder : results from the ENIGMA major depressive disorder working group. *Molecular Psychiatry* 26 : 5124–5139, 2021.
- Harvanek ZM, Fogelman N & Sinha R. Psychological and biological resilience modulates the effects of stress on epigenetic aging. *Translational Psychiatry* 11(601) : 1–9, 2021.
- Hewitt G, Jurk D, Marques FDM, Melo CC, Hardy T, Gackowska A, Anderson R, Taschuk M, Mann J & Passos JF. Telomeres are favoured targets of a persistent DNA damage response in ageing and stress-induced senescence. *Nat Commun* 3(708) : 1–9, 2012.
- Jiang S, Postovit L, Cattaneo A, Binder EB, & Aitchison

- KJ. Epigenetic Modifications in Stress Response Genes Associated With Childhood Trauma. *Front Psychiatry* 10 (808) : 1–19, 2019.
- Kiecolt–Glaser J, Preacher KJ, MacCallum RC, Atkinson C, Malarkey WB & Glaser R. Chronic stress and age–related increases in the proinflammatory cytokine IL–6. *PNAS* 100(15) : 9090–9095, 2003.
- Klopach ET, Crimmins EM, Cole SW, Seeman TE, & Carroll JE. Social stressors associated with age–related T lymphocyte percentages in older US adults : Evidence from the US Health and Retirement Study. *PNAS* 119 (25) : 11–5, 2022.
- Kupriyanov R & Zhdanov R. The eustress concept : problems and outlooks. *World Journal of Medical Sciences* 11 (2) : 179–185, 2014.
- Madison AA, Belury MA, Andridge R, Renna ME, Shrout MR, Malarkey WB, Lin J, Epel ES & Kiecolt–Glaser JK. Omega–3 supplementation and stress reactivity of cellular aging biomarkers : an ancillary substudy of a randomized, controlled trial in midlife adults. *Molecular Psychiatry* 26 : 3034–3042, 2021.
- Maynard S, Fang EF, Scheibye–Knudsen M, Croteau DL & Bohr VA. DNA Damage, DNA Repair, Aging, and Neurodegeneration. *Cold Spring Harb Perspect Med* 5 (10) : 1–18, 2015.
- Gibney E & Nolan C. Epigenetic and gene expression. *Heredity* 105 : 4–13, 2010.
- O'Connor TM, Halloran DJO & Shanahan F. The Stress Response and the Hypothalamic–Pituitary–Adrenal Axis : From Molecule to Melancholia. *QJM* 93(6) : 323–333, 2000.
- Oei NYL, Jansen SW, Veer IM, Slagboom PE, Grond J & Heemst D. Stress evokes stronger medial posterior cingulate deactivations during emotional distraction in slower paced aging. *Biol Psychol* 135 : 84–92, 2018.
- Paudel D, Morikawa T, Yoshida K, Uehara O, Giri S, Neopane P, Khurelchuluun A, Hiraki D, Sato J & Abiko Y. Chronic stress–induced elevation of IL–1 β in the saliva and submandibular glands of mice. *Med Mol Morphology* 53 : 238–243, 2020.
- Paudel D, Kuramitsu Y, Uehara O, Morikawa T, Yoshida K, Giri S, Islam ST, Kitagawa T, Kondo T, Sasaki K, Matsuoka H, Miura H & Abiko Y. Proteomic and microbiota analyses of the oral cavity during psychological stress. *PLoS ONE* 17(5) : 1–18, 2022.
- Reed RG. Stress and immunological aging. *Curr Opin in Behav Scien* 28 : 38–42, 2019.
- Scott SB, Graham–Engeland JE, Engeland CG, Smyth JM, Almeida DM, Katz MJ, Lipton RB, Mogle JA, Munoz E, Ram N & Sliwinski MJ. The effects of stress on cognitive aging, physiology and emotion (ESCAPE) project. *BMC Psychiatry* 15 : 146, 2015.
- Seo JS, Lee KW, Kim TK, Baek IN, Im JY & Han PL. Behavioral stress causes mitochondrial dysfunction via ABAD up–regulation and aggravates plaque pathology in the brain of mouse of Alzheimer disease. *Free Rad Bio and Med* 50(11) : 1526–1535, 2011.
- Sharpley CF. Neurobiological Pathways between Chronic Stress and Depression : Dysregulated Adaptive Mechanisms. *Clinical Medicine : Psychiatry* 2009(2) : 33–45, 2009.
- Sheth C, McGlade E & Yurgelun–Todd D. Chronic stress in adolescents and its neurobiological and psychopathological consequences : An RDoc Perspective. *SAGE Journals* 1 : 1–22, 2017.
- Simon NM, Smoller JW, McNamara KL, Maser RS, Zalta AK, Pollack MH, Nierenberg AA, Fava M & Wong KK. Telomere shortening and mood disorders : preliminary support for a chronic stress model of accelerated aging. *Biol Psychiatry* 60(5) : 432–435, 2006.
- Spektor AM, Postolache TT, Akram F, Scott AJ, Wadhwani A, Mark A, & Reynolds MA. Psychological Stress : A Predisposing and Exacerbating Factor in Periodontitis. *Current Oral Health Reports* 7 : 208–215, 2020.
- Tyrka AR, Price LH, Kao HT, Porton B, Marsella SA & Capenter LL. Childhood Maltreatment and Telomere Shortening : Preliminary support for an effect of early stress on cellular aging. *Biological Psychiatry* 67(6) : 531–543, 2010.
- Villalobos V, Garrido M, Reyes A, Fernandez C, Diaz C, Torres VA, Gonzalez PA & Caceres M, et al. Aging envisage imbalance of the periodontium : A keystone in oral disease and systemic health. *Front. Immunol* 13 (1044334) : 1–8, 2022.
- Yegorov YE, Poznyak AV, Nikiforov NG, Sobenin IA & Orekhov AN. The link between chronic stress and accelerated aging. *Biomedicines* 8(7) : 1–14, 2020.
- Zannas AS, Jia M, Hafner K, Baumert J, Wiechmann T, Pape JC, Arloth J, Ködel M, Martinelli S, Roitman M, Röh S, Haehle A, Emeny RT, Iurato S, Carrillo–Roa T,

Lahti J, Räikkönen K, Eriksson JG, Drake AJ, Waldenberger M, Wahl S, Kunze S, Lucae S, Bradley B, Gieger C, Hausch F, Smith AK, Ressler KJ, Müller-Mysok B, Ladwig KH, Rein T, Gassen NC, & Binder EB. Epigenetic upregulation of FKBP5 by aging and stress contributes to NF- κ B-driven inflammation and cardiovascular risk. *PNAS*, 116(23) : 11370–11379, 2019.

Zannas AS, Arloth J, Roa TC, Lurato S, Roh S, Ressler KJ, Nemeroff CB, Smith AK, Bradley B, Heim C, Menke A, Lange JF, Bruckl T, Ising M, Wray NR, Erhardt A, Binder EB & Mehta D. Lifetime stress accelerates epigenetic aging in an urban, African American cohort : relevance of glucocorticoid signaling. *Genome Biology* 16 (266) : 1–12, 2015.