

SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

The effect of sour cherry anthocyanins on oral health

by Dr. Skopkó Boglárka Emese

Supervisors:

Dr. Judit Remenyik and Dr. Kinga Ágnes Bágyi



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By Boglárka Emese Skopkó, DMD (Doctor of Dental Medicine)

Supervisors: Dr. Judit Remenyik PhD and Dr. Kinga Ágnes Bágyi PhD

Doctoral School of Dental Sciences, University of Debrecen

Head of the Defense Committee:	Pál Péter Nánási PhD, Dsc
Reviewers:	Kinga Mónika Turzó PhD Éva Julianna Leiter PhD
Members of the Defense Committee:	Árpád Kovács PhD Anette Stájer PhD

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1. INTRODUCTION

There are many chemical and mechanical methods of modulating the oral microbiome. Our goal was to find methods that can be easily carried out by patients at home, and to beneficially influence the oral microbiome, and to investigate the protective factors found in saliva that play a role in maintaining oral health, as well as biomarkers suitable for monitoring oral health.

The production of pro-inflammatory cytokines is a complex process, which is induced by the immune response to the oral microorganisms (e.g., bacterial lipopolysaccharide (LPS)). Based on the complex interactions between cytokines and mucins, the effects of natural products can be easily followed by salivary sampling.

Melatonin - which is produced in the pineal gland – is an endogenous antioxidant, which is also excreted into the saliva and its level is changing by the circadian rhythm of the human body. The salivary melatonin has a very potent antioxidant activity, which can be observed during the carious process by its anticariogenic activity.

Several factors exist in saliva, which are important in the protection of teeth and help in the maintenance of the commensal oral microbiota and prevent the proliferation of pathogenic microorganism. The mucins are predictors of the imbalance in the oral cavity and the inflammatory cytokines are initiators of the defence processes. The mucins play a protective role in this process.

Mucins have several roles, the most important may be that they can help the growth, adhesion, protection or swallowing of microorganism, hence they can maintain the sialo-microbial-dental equilibrium. The pellicle formation - which is the base of the plaque accumulation – starts from the 'polymicrobial aggregates' found in the human saliva. Microorganisms can also be attached to salivary macromolecules (e.g. mucins), which help their removal from the mouth by swallowing hence protect the oral cavity. Mucins are also beneficial on the commensal oral microbiota, as they have prebiotic function, which helps their proliferation.

The pigments of the cherry (*Prunus cerasus* L.) are anthocyanins (AC), which, due to their beneficial effects on health due to their antioxidant properties, have shown positive results in the treatment of many diseases (e.g. tooth decay). It is well known that sour cherry can inhibit the growth of antibiotic-resistant forms of *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, and it is also effective against *Fusobacterium nucleatum* and *Candida albicans*. During the course of health benefits of sour cherry anthocyanins (AC) they can reduce the number of *S. mutans* counts and α -amylase activity of saliva.

AIMS

We aimed to investigate the action of anthocyanin containing chewing gum and toothbrush change:

-The 2-week effect of chewing (daily 3 times) sour cherry gum and toothbrush change in young adult (AG I, 18-30) and adult (AG II, 31-45) population with healthy oral status on cytokine mRNA (messenger Ribonucleic Acid) (IL-1 β , TNF α) and protein levels (IL-1 β , IL-2, IL-4, IL-6, TNF α), on the level of secreted mucins (MUC5B and MUC7), melatonin and Ca²⁺ ion levels in unstimulated and stimulated saliva samples.

- After the control period (1-week), the effect of scaling and toothbrush change on the level of these biomarkers (cytokines, mucins, melatonin), ions and the 16 S rRNA analysis of unstimulated and stimulated saliva samples.

-Studying the correlation between the salivary cytokines, mucins, melatonin and salivary microbiota.

MATERIALS AND METHODS

Ethical permission was accepted by ETT TUKEB, Hungary (licence number: IV/1120-1/2020/EKU) recommended by the DE KK RKEB/IKEB (Regional Ethical Committee) (protocol number: 5379-2019) University of Debrecen based on the principles of World Medical Association Declaration of Helsinki. A study registration on the <https://clinicaltrials.gov/> was also made under the number 2022-IV/1120-1/2020. The experiment was an open-label, self-control, multi-centre study conducted between the Faculty of Dentistry, Center for Complex Systems and Microbiome Innovations and the Faculty of Pharmacy at the University of Debrecen.

The participants were people between the ages of 18 and 45 with good oral hygiene and good general health, who were divided into two age groups: the members of age group I were between 18 and 30 years old, and the members of age group II were between 30 and 45 years old. Whenas we informed them verbally about the sampling, the Patient Information and the Consent Statements were issued, and by reading them the sampling began with the written consent of the participants.

All of the participants accepted and signed the consent statement after explanation of the study conditions, by accentuation that their consent is free and they can stop the participation at any time of the experiments. They were asked to inform us immediately in case of any infection treated by antibiotics or non-steroidal anti-inflammatory drugs (NSAIDs). The patients were encoded by numbers, because of patients' rights.

The study was a self-control experiment, combined from baseline (B), first week: follow-up 1 (: F1) and second week: follow-up 2 (: F2) were conducted by chewing the gum with sour cherry extract.

Before the first occasion general and dental status, basic periodontal examination about the study participants was recorded on a status chart containing rubrics for the dental status, basic periodontal examination, plaque and calculus indices. [28]

The participants got their chewing tablets at the beginning of each week. After the control (Baseline, B) period a scaling was made on the Day 7 of control week, then the participants got the sour cherry chewing gums and they were asked to chew them daily 3 times for 1-5 minutes after the tooth-brushing followed by the main dishes for a period of 2 weeks. The sampling occasions were on the Day 1, Day 4 and Day 7 of the study weeks (where the Day 7 of a week was the same as the Day 1 of the forthcoming week during the 2-week chewing gum usage)

between 11:00 a.m. and 14:00 p.m. based on the study protocol in our earlier experiment considering the circadian rhythm of the body in the determination of the sampling hour.

The stimulated saliva samples were taken in a different time following the same protocol as the unstimulated supplemented by chewing of a gum without active (AC) ingredient during the 3-week experimental period. 1-1 ml saliva was taken from each patient during an occasion, and they were sent into the Labs of Center for Complex Systems and Microbiome Innovations (KRÉMK), where samples were taken into freezer (-80 °C) to use them during later processing.

The participants were people between the ages of 18 and 45 with good oral hygiene and good general health, who were divided into two age groups: the members of age group I were between 18 and 30 years old, and the members of age group II were between 30 and 45 years old. The half of the participants (10 persons) were asked to change their toothbrush after scaling another half (10 persons) did not change the toothbrush after scaling.

Sour cherry chewing gum and placebo chewing gum were produced in the Department of Pharmaceutical Technology, which is licenced to produce sour-cherry containing chewing gums. The sour cherry extract was prepared from the Hungarian sour cherry (*Prunus cerasus* L.) variety “VN1”, a selection of “Csengődi csokros”.

We performed ELISA (enzyme-linked immunosorbent assay) - Mucin-5B (MUC5B), Mucin 7 (MUC7), Interleukin-1 β (IL-1 β), Tumor necrosis factor α (TNF α), Interleukin-2 (IL-2), Interleukin-6 (IL-6), melatonin -; qPCR (polymerase chain reaction) measurements - Interleukin-1 β (IL-1 β), Tumor necrosis factor α (TNF α) -; Ca²⁺ level determination and the same way as in our earlier study, 16 S rRNA metagenome sequencing [only on sampling days: B (baseline) day 4, F1 (follow-up 1): day 11 and F2 (follow-up 2): day 21] during our investigation.

During the 16S rRNA sequencing Illumina MiSeq benchtop sequencer was used for the sequencing of the V3 and V4 hypervariable regions of bacterial 16S rRNA gene.

Naïve Bayesian machine learning based classifier was used for taxonomic alignment with the Human Oral Microbiome Database (HOMD, <http://homd.org/>, ver.: 15.23. accessed 2023.08.01.). To analyse 'alpha diversity' Chao1, Faith, Shannon and Simpson indexes were calculated in the QIIME 2 (version: 2021.8) pipeline (<https://qiime2.org/>). The calculation and visualization of the heat tree matrix wer made with Metacoder package in R. To determine the effects of AC gum chewing core microbiomes were made by considering operational taxonomic units (OTUs) represented in 100% of all saliva samples. We performed cluster analysis in

relation to the bacterial genera with the relative gene expression and protein concentrations of mucins, cytokines and melatonin using Pearson correlation.

RESULTS

According to the age groups the average age of AG I. (age group I.) was 26.1 ± 1.91 , the DMF-T was 4.9 ± 4.38 , in the AG II. (age group II.) the average age was $36,3 \pm 3.83$ and the DMF-T was 8.9 ± 4.91 . Pearson correlation showed significant, negative correlation (-0.48) between the DMF-T ($6,9 \pm 4,97$) and BPE ($0,43 \pm 0,34$) of the participants.

Pro-inflammatory cytokines, mucins and melatonin levels in unstimulated and stimulated saliva

Comparison of unstimulated and stimulated saliva

The calcium levels showed significant difference in stimulated saliva between the control and 11th day of sampling ($p=0.0002$).

When we compared the unstimulated and stimulated saliva we found significant differences between the two groups except the IL-1 β and IL-2. In stimulated saliva the MUC5B, IL-1 β mRNA, TNF α , TNF α mRNS, melatonin, MUC7, TNF α and Ca²⁺ was significantly - while IL-1 β was not significantly – higher, and IL-6 was significantly higher in the unstimulated saliva.

The effects of toothbrush change

Unstimulated saliva

We could observe significant differences in values of TNF α and MUC7 on the first sample occasion of chewing the anthocyanin gum.

The IL-1 β mRNA expression also showed significant differences between the two groups and by the values of BR group, otherwise till the end of experiment it was reduced in both groups, hence the mRNA was completely used for the protein synthesis.

The results of the Pearson correlation showed significant, negative correlation (-0.95) between the IL-2 and MUC7 in case of NBR. Further significance could be seen in this group between IL-2 and melatonin (0.96).

Stimulated saliva

In stimulated saliva in case of MUC5B all values of the NBR were significantly lower than the BR. We could see similar results in the values of melatonin, where the control of BR (11.7) was significantly higher than the Day 10 (7.43) of NBR. Further significant differences could be observed in case of IL-6, where the values of BR were generally lower than in the NBR.

These results were shown by the Pearson correlation, where in the BR the IL-6 and MUC5B (0.95), IL-6 and melatonin (0.98), MUC5B and melatonin (0.9) were positively correlated with each other, while in the NBR the IL-2 and IL-6 significantly, negatively (-0.91) correlated with each other.

The results of 16S rRNA sequencing in unstimulated and stimulated saliva

Alpha diversity

As alpha diversity regards, Chao1 scores of the pooled saliva samples on Figure 2 showed a mild increase during F1 (follow-up 1) in comparison to the baseline (B) and to F2 (follow-up 2) group, which proved to be not significant ($p > 0.05$).

When we compared the unstimulated and stimulated saliva (*Chao1*, *Faith's PD*, *Shannon és Simpson*) we found greater values in unstimulated saliva (B_US, AC_US), as in the stimulated saliva (B_S, AC_S).

Regarding the stimulated saliva the *Chao1* and *Shannon* diversities definitely showed that the NBR group had a lower diversity, than the BR, but these results were not significant. Regarding the *Faith* and *Simpson* diversities minor differences could be observed between the two groups by toothbrush change, but the tendency was the same.

Beta diversity

In order to investigate community shifts in the core oral microbiota, taxonomic heat tree has been made to reveal effects of toothbrush change. The Wilcoxon rank sum test showed significant differences in community compositions.

Correlation of DMF-T with detected genera in unstimulated saliva

We investigated the correlations between the 20 most abundant genera [*Clostridia_UCG.014* (0.528), *Prevotella* (0.322), *Fusobacterium* (0.224), *Selenomonas* (0.228), *Oribacterium* (0.289) *Lachnoanaerobaculum* (-0.622), *Neisseria* (-0.436), *Porphyromonas* (-0.254) and *Granulicatella* (-0.205)] and DMF-T values of the study population.

Log₂ proportions of remarkable families and genera of the salivary microbiota

In both groups the highest log₂ proportions were observed for the family of *Fusobacteriaceae* (NBR/B: 2.207, BR/B: 2.206) followed by *Cardiobacteriaceae* (NBR/B: 1.31, BR/B: 1.446) and the same tendencies could be observed in the genus *Fusobacterium* (NBR/B: 2.207, BR/B: 2.206) and *Cardiobacterium* (NBR/B: 1.31, BR/B: 1.446) during the control as compared to the periods of chewing gum usage.

Log₂ proportions of potential biofilm forming genera

The genera *Absconditabacteria_(SR1)_[G_1]*, *Corynebacterium*, *Fusobacterium* and *Saccharibacteria_(TM7)_[G-5]* showed the highest log₂ ratios in the NBR, while the BR contained mainly *Leptotrichia*, *Neisseria* and *Haemophilus*.

Relative frequency of detected species in unstimulated saliva

According to the heatmap the most frequent species were the *Prevotella melanogenica*, *Porphyromonas pasteri*, *Rothia mucilaginosa*, *Haemophilus parainfluenzae*, *Veillonella atypica*, *Veillonella dispar* and *Veillonella rogosae*.

Microbial networks in groups by toothbrush change in unstimulated saliva

The genus *Streptococcus* in NBR, it is more likely to have strong positive association with the genus *Gemella* (0.99), which could be found in caries active patients, it had also positive

association with *Neisseria* (0.99), *s_Neisseria perflava* (0.95) and *Haemophilus* (0.79) in this group. Comparing the positively associated network relationships of the genus *Streptococcus* in the BR group was the part of the purple cluster, where it showed the highest positive association with mainly, the health associated *Prevotella veroralis* (0.95), *Granulicatella* (0.94) and *Rothia* (0.92).

Core microbiome in stimulated saliva

The 100% Core oral microbiota between the participants according to the average of their relative frequency: *Streptococcus* (0.55), *Prevotella* (0.14), *Veillonella* (0.13), *Neisseria* (0.056), *Granulicatella* (0.022), *Saccharibacteria_(TM7)_[G_1]* (0.021), *Gemella* (0.03), *Leptotrichia* (0.036).

Correlation of the microbiota with cytokines, mucins and melatonin

The MUC5B and melatonin both showed positive correlation with *g_Lachnospiraceae_[G-2]* (MUC5B: 0,167, melatonin: 0,021), *g_Eikenella* (MUC5B: 0,658, melatonin: 0,744) and *g_Saccharibacteria_(TM7)_[G-5]* (MUC5B: 0,658, melatonin: 0,743).

The IL-1 β had a negative correlation with the *g_Streptococcus* (-0,463), on the other hand, it had a positive correlation with its mRNA (0,603).

DISCUSSION

According to the age groups the average age of AG I. (age group I.) was 26.1 ± 1.91 , the DMF-T was 4.9 ± 4.38 , in the AG II. (age group II.) the average age was $36,3 \pm 3.83$ and the DMF-T was 8.9 ± 4.91 .

The average age of the BR group (10 participants did not changing the toothbrush after scaling) was 32 ± 6.1 and here the average of DMF-T was 8.11 ± 4.64 . The average age of the NBR group (10 participants changing the toothbrush after scaling) was 31.4 ± 5.6 and the average DMF-T was 5.22 ± 4.5 in this group.

Pearson correlation showed significant, negative correlation (-0.48) between the DMF-T ($6,9 \pm 4,97$) and BPE ($0,43 \pm 0,34$) of the participants.

Pro-inflammatory cytokines, mucins and melatonin levels in unstimulated saliva

In unstimulated saliva we could observe significant difference in case of IL-1 β between the BR and NBR groups by toothbrush change. We could observe further significant differences in values of TNF α and MUC7 on the first sample occasion of chewing the anthocyanin gum.

The IL-1 β mRNA expression also showed significant differences between the two groups and by the values of BR group, hence the mRNA was completely used for the protein synthesis.

These results are explained by the fact that scaling after the control period significantly reduces the number of microorganisms in the oral cavity, after which, based on the available literature data, plaque formation can start again from saliva and during nutrition or oral hygiene activities, so if the used toothbrush is not replaced, it is listed as an aggravating factor. In accordance with this, the significantly higher values of IL-1 β and TNF α protein concentrations show that if the toothbrush is not replaced, the used toothbrush maintains inflammation in the oral cavity. The increased value of MUC7 in this group may indicate that with the increased number of microorganisms, their removal also starts.

Analysis of unstimulated salivary microbiota in our study population

In our study 4 days after scaling the results of Chao 1 diversity showed us that the supplement of oral hygiene habits with anthocyanin containing chewing gum usage can help to restore and maintain a stable and diverse microbiome.

The toothbrush change resulted higher relative frequency of the genera *Neisseria* and *Haemophilus* on heat-trees by Metacoder and we found also different clusters by toothbrush change, which was not represented by the treatment time, so we can conclude that the toothbrush change has an impact on the microbiome composition.

In our study according to the Pearson correlation higher prevalence of the genus *Porphyromonas* can be connected to lower DMF-T values. *Granulicatella*, *Neisseria* and *Porphyromonas* are health associated bacterial genera, which are also connected to lower DMF-T values in our experiment (*Granulicatella*: -0.205, *Neisseria*: -0.436 and *Porphyromonas*: -0.254).

As the green cluster in our network analysis in NBR group represents a possible metabolic pathway of hydrogen peroxide from *Streptococci* which were in positive associations with *Neisseria* and *Haemophilus parainfluenzae* who can use the hydrogen peroxide produced by *Streptococci* (e.g. *Streptococcus sanguinis*) and the potential caries active *Gemella* genus. In the BR group the *Streptococci* were found in the purple cluster, where they were in stronger association with health associated bacteria (*Prevotella veroralis*, *Granulicatella*).

We found lower level of *Prevotella melanogenica*, *Porphyromonas pasteri*, *Fusobacterium nucleatum subsp. vincentii* and *Rothia mucilaginosa* in subjects who changed the toothbrush after scaling.

Comparative study of the levels of proinflammatory cytokines and mucins in saliva

Against the background of these results, the significantly higher values of MUC5B and melatonin detected in non-toothbrush changers show that the composition of the microbiome changes as a result of toothbrush change in such a way that the level of protective factors (MUC5B, melatonin) will be higher, which in the case of melatonin is higher than in people with low caries frequency also supports its concentration.

Analysis of salivary microbiota in our study population

In stimulated saliva the *alpha* diversity definitely showed that the NBR group had a lower diversity than the BR. The beta diversity showed late colonizers and in the BR group non-mutans streptococci.

We performed the correlation of mucins, melatonin and cytokines with stimulated salivary microbiota.

The *g_Ruminococcae_[G-2]* (0,36) and *g_Ruminococcae_[G-1]* (0,32) less, but it was positively correlated with MUC7, otherwise this genera is able to use the mucins as carbon source, on the other hand for their further utilization the existence of complex microbial community is important. Based on the literature, the *g_Bifidobacterium* also contains the whole set of mucine degrading enzymes and also correlated positively with MUC7. The *Haemophilus* was correlated positively with MUC7 – the difference between the two main soluble mucins -, furthermore its positive correlation with IL-6 strengthens the cariogenic role of this genus.

The *g_Lachnospiraceae_[G-2]*, *g_Eikenella* and *g_Saccharibacteria_(TM7)_[G-5]* was correlated positively with both the MUC5B and both the melatonin.

Our results strengthen the melatonin producing effect of these bacterial genera.

The IL-6 showed a small positive correlation with *Prevotella* (0,162), TNF α also showed positive correlation with *g_Prevotella* (0,607) in stimulated saliva, which is in line with earlier literature which found *Prevotella* as *pathognomy* to gingivitis.

Our present data are contradictory with these finding as we found a positive correlation of IL-1 β mRNA (0,603) and a negative of IL-1 β (-0,463) with the *g_Streptococcus*.

Comparison of unstimulated and stimulated saliva

In stimulated saliva the MUC5B, IL-1 β mRNA, TNF α , TNF α mRNS, melatonin, MUC7, TNF α and Ca²⁺ was significantly - while IL-1 β was not significantly – higher, and IL-6 was significantly higher in the unstimulated saliva. Stimulated saliva also has a higher anticariogenic potential, which is also consistent with our studies, where we measured significantly higher levels of MUC5B, MUC7, TNF α and melatonin in the stimulated saliva.

SUMMARY

We analyzed the changes in the protective and inflammatory components of saliva and the microbiota. In the case of protective factors, we could observe changes in their expression level. The connecting medium between saliva, teeth and microbiota is a biofilm that has aggregated microbial units and after complete supra- and subgingival plaque and calculus removal, the formation of the acquired pellicle covering the teeth starts from the saliva within 4 hours after brushing. Scaling also involves the formation of microwounds, to which the body responds by producing inflammatory factors. In our study, we could also classify the scaling, the replacement of a used toothbrush and the use of chewing gum without active ingredients among the mechanical effects, the effects of which add up, and it is important to highlight that both our mechanical and chemical interventions primarily had an effect on the microbiota, the consequent changes of which we could see it in changes in the levels of protective factors and proinflammatory cytokines. In our studies, in line with previous studies, we also proved that cherry anthocyanins have beneficial effects on the oral microbiota. Based on the analysis of the resting and stimulated saliva cytokine profile, mucin and Ca^{2+} levels, as well as the analysis of the microbiota, we can state that scaling and the subsequent toothbrush exchange have a beneficial effect on both unstimulated and stimulated saliva. Based on all of this, we can state that the factors we examined are biomarkers suitable for monitoring oral health.

NEW SCIENTIFIC RESULTS

- 1) In our study, calculus removal increased microbial alpha diversity maintained by anthocyanin in unstimulated saliva.
- 2) The level of TNF α was decreased due to the AC treatment.
- 3) *Prevotella melaninogenica*, *Porphyromonas pasteri*, *Fusobacterium nucleatum subsp. vincentii* and *Rothia mucilaginosa* species levels were lowered in unstimulated saliva samples of subjects who changed their toothbrush after calculus removal.
- 4) In the case of MUC7 - which play an important role in lubrication and protection against bacteria- we also observed its positive correlation with bacteria (*g_Ruminococcaceae*, *g_Bacteroidetes*, *g_Bifidobacterium*, *g_Haemophilus*).
- 5) Three genera: *g_Lachnospiraceae [G-2]*, *g_Saccharibacteria (TM7) [G-5]*, *g_Eikenella* - are positively correlated with MUC5B and melatonin, their melatonin-producing ability also supports the complex interactions between oral microbiota and protective factors proves its role by serving as a prebiotic and nutrient source for bacteria, which ensures the balance of the commensal flora.
- 6) In accordance with the results of Hungarian authors, the positive correlation between *g_Prevotella* and inflammatory factors in stimulated saliva should be highlighted, which supports its role in inflammation.
- 7) In the case of *Streptococcus*, which plays a significant role in dental caries, their different network connections observed in unstimulated saliva with or without toothbrushing (*Gemella*, *Neisseria*, *Haemophilus*) should be highlighted in the sense that without toothbrushing, their survival and the formation of a potentially more cariogenic microenvironment can be assumed.
- 8) Their positive correlation with MUC7 seems to clearly support that MUC7 has a protective role against this bacterial genus.
- 9) It should be noted that the levels of Ca²⁺, MUC5B, MUC7, TNF α and melatonin are significantly higher in stimulated saliva than in unstimulated saliva, which proves that as a result of the masticatory stimulus, the bacteria become planktonic, followed by an increase in the level of protective factors, thus maintaining the balance of the flora.
- 10) The significant increase of MUC7, IL-1 β mRNS and protein, as well as the TNF α protein was observed in unstimulated saliva in the group without toothbrush change.

11) This confirms that the more cariogenic environment maintained by the toothbrush leads to an increase in the levels of these proinflammatory cytokines and the antibacterial MUC7 in healthy individuals. And in stimulated saliva, the significantly higher level of MUC5B and melatonin levels detected in toothbrush changers can be explained by the different antibacterial and prebiotic role of MUC5B and the increase in melatonin levels caused by bacterial activity.

BIBLIOGRAPHY



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Subject: PhD Publication List

Candidate: Boglárka Emese Skopkó
Doctoral School: Doctoral School of Dental Sciences

List of publications related to the dissertation

1. **Skopkó, B. E.**, Homoki, J., Fazekas, M., Paholcsek, M., Fauszt, P., Dávid, P., Stündl, L., Bíróné Molnár, P., Forgács, I. N., Váradi, J., Bágyi, K., Gálné Remenyik, J.: Changes in the Composition of Unstimulated and Stimulated Saliva Due to Chewing Sour Cherry Gum and a Toothbrush Change.
Cells. 13 (3), 1-29, 2024.
DOI: <http://dx.doi.org/10.3390/cells13030251>
IF: 5.1 (2023)
2. **Skopkó, B. E.**, Paholcsek, M., Szilágyi-Rácz, A. A., Fauszt, P., Dávid, P., Stündl, L., Váradi, J., Kovács, R. L., Bágyi, K., Gálné Remenyik, J.: High-Throughput Sequencing Analysis of the Changes in the Salivary Microbiota of Hungarian Young and Adult Subpopulation by an Anthocyanin Chewing Gum and Toothbrush Change.
Dentistry Journal. 11 (2), 1-16, 2023.
DOI: <http://dx.doi.org/10.3390/dj11020044>
IF: 2.5





List of other publications

3. **Skopkó, B. E.**, Deák, Á., Matesz, K., Kelentey, B., Bácskai, T.: Pefloxacin induced changes in serotonergic innervation and mast cell number in rat salivary glands.
Drug Chem. Toxicol. 43 (5), 496-503, 2020.
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03 October, 2024



List of publications and conferences:

Lectures connected to this thesis:

1. XX. TISZÁNTÚLI AGRÁRTUDOMÁNYI NAPOK

MEGGY ANTHOCYANINOK SZÁJÜREGI EGÉSZSÉGRE KIFEJTETT HATÁSAI

Effect of sour cherry anthocyanins in oral health

Boglárka Emese Skopkó¹; Judit Rita Homoki²; Mónika Éva Fazekas²; Melinda Paholcsek²; Péter Fauszt²; Péter Dávid²; László Stündl²; Piroska Bíró²; Ildikó Noémi Forgács²; Judit Váradi³; Kinga Ágnes Bági^{1†} és Judit Remenyik^{2,*†}

2. A Magyar Mikrobiológiai Társaság 2022. évi Nagygyűlése és a XV. Fermentációs Kollokvium, 2022.10.12.-14.

EFFECT OF SOUR CHERRY ANTHOCYANINS ON HEALTHY HUMAN ORAL MICROBIOME

Boglárka Emese Skopkó¹, Melinda Paholcsek², Anna Anita Szilágyi-Rácz², Péter Fauszt², Péter Dávid², Judit Rita Homoki², Mónika Éva Fazekas², Piroska Bíró², László Stündl², Judit Váradi², Gábor Vasvári³, Renátó Kovács⁴, Kinga Ágnes Bági⁵, Judit Remenyik²

Posters connected to this thesis:

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EFFECT OF SOUR CHERRY ANTHOCYANINS ON HEALTHY HUMAN ORAL MICROFLORA (A PILOT CLINICAL STUDY),

B.E. Skopko¹, M.E. Fazekas², J.R. Homoki², J. Remenyik², M. Paholcsek³, K.A. Bági⁴

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The interaction of anthocyanin containing chewing gum and toothbrush microbiota on the salivary microbiota of Hungarian young adults after scaling

Boglárka Emese Skopkó¹, Melinda Paholcsek², Anna-Anita Szyilágyi-Rácz², Péter Fauszt², Péter Dávid², Judit Rita Homoki², Mónika Éva Fazekas², Piroska Bíró², László Stündl², Judit Váradi³, Gábor Vasvári³, Renátó Kovács⁴, Kinga Ágnes Bági⁵, Judit Remenyik²

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