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MORPHOFUNCTIONAL EFFECTS OF THE COMBINED EXPOSURE TO SODIUM NITRITE, MONOSODIUM GLUTAMATE, AND PONCEAU 4R ON THE DIGESTIVE SYSTEM

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The widespread use of sodium nitrite, monosodium glutamate, and synthetic food colorants necessitates a comprehensive assessment of their effects on the digestive system, particularly under conditions of simultaneous exposure to several food additives. The aim of this review was to synthesize current experimental and analytical evidence on the morphofunctional effects of combined sodium nitrite, monosodium glutamate, and Ponceau 4R exposure on the digestive organs and to identify the potential mechanisms underlying the observed alterations. A structured literature search was performed in major international bibliographic databases, followed by screening, eligibility assessment, and qualitative synthesis in accordance with PRISMA principles. Thirty-two publications were included in the final analysis, comprising experimental animal studies, systematic and narrative reviews, and analytical studies addressing food additive exposure and control. The evidence indicates that combined exposure is associated with structural remodeling of the gastric and intestinal mucosa, alterations of intestinal villi and submucosal glands, changes in the hemomicrocirculatory bed, hepatic parenchymal injury, and salivary gland alterations. In parallel, food additives may affect gut microbiota composition, intestinal barrier integrity, metabolic homeostasis, inflammatory signaling, and oxidative balance. The available evidence supports the concept that the safety of food additives should be evaluated not only individually but also in the context of their combined exposure and potential interactions.

Key words: food additives, sodium nitrite, monosodium glutamate, Ponceau 4R, digestive system, gut microbiota, morphofunctional changes.

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МОРФОФУНКЦІОНАЛЬНІ ЕФЕКТИ КОМБІНОВАНОГО ВПЛИВУ НІТРИТУ НАТРІЮ, ГЛУТАМАТУ НАТРІЮ ТА ПОНСО 4R НА ТРАВНУ СИСТЕМУ

Поширене використання нітриту натрію, глутамату натрію та синтетичних харчових барвників зумовлює необхідність комплексної оцінки їхнього впливу на травну систему, особливо за умов одночасного надходження кількох харчових добавок. Метою огляду було узагальнити сучасні експериментальні та аналітичні дані щодо морфофункціональних ефектів комбінованої дії нітриту натрію, глутамату натрію та понсо 4R на органи травної системи, а також визначити потенційні механізми формування патологічних змін. Проведено структурований пошук наукових публікацій у міжнародних бібліографічних базах із наступним скринінгом, оцінкою відповідності критеріям включення та якісним синтезом результатів відповідно до принципів PRISMA. До фінального аналізу включено 32 джерела, серед яких експериментальні дослідження на лабораторних тваринах, систематичні та наративні огляди, а також роботи, присвячені аналітичному контролю харчових добавок. Встановлено, що комбінована експозиція асоціюється зі структурною перебудовою слизової оболонки шлунка і кишечника, змінами ворсинок, підслизових залоз, гемомікроциркуляторного русла, паренхіми печінки та слинних залоз, а також із порушеннями кишкового мікробіому, метаболічного гомеостазу, бар'єрної функції та локальних запально-окиснювальних процесів. Сукупність даних свідчить про необхідність оцінювати безпеку харчових добавок не лише ізольовано, а й у контексті їхньої комбінованої дії.

Ключові слова: харчові добавки, нітрит натрію, глутамат натрію, понсо 4R, травна система, кишковий мікробіом, морфофункціональні зміни.

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Food additives are an integral component of the modern food industry, where they are used to regulate the flavor, technological, organoleptic, and microbiological properties of food products. The increasing proportion of processed and ultra-processed foods in the diet is accompanied by greater duration and frequency of exposure to various classes of food additives, raising concerns regarding their biological safety [14, 21, 27–29]. Current research indicates that the consequences of such exposure are

not limited to individual metabolic or toxicological effects but may involve the intestinal epithelium, mucosal barrier, microbiota, immune mechanisms, liver, and other organs and components of the digestive system [1, 14, 21, 27].

Particular interest has been focused on the combined effects of sodium nitrite (E250), monosodium glutamate (E621), and the synthetic azo dye Ponceau 4R (E124). These compounds belong to different functional groups of food additives and have

fundamentally different technological properties; however, they may enter the body simultaneously through real-world food consumption. Sodium nitrite is used primarily as a preservative and color stabilizer, monosodium glutamate as a flavor enhancer, and Ponceau 4R as a synthetic colorant. The combination of substances with different mechanisms of biological activity creates a challenge in assessing their potential cumulative or mutually potentiating effects.

Sodium nitrite is a source of the nitrite ion, which participates in numerous redox reactions. Excessive exposure may be accompanied by increased oxidative stress and alterations in antioxidant defenses and inflammatory responses. Experimental studies have demonstrated that sodium nitrite may induce morphofunctional abnormalities not only in the liver but also in the salivary glands and other organs [2, 3, 10, 11, 24]. At the same time, studies involving antioxidant and plant-derived compounds further support the importance of oxidative and inflammatory mechanisms in nitrite-induced injury [2, 10, 11, 24].

Monosodium glutamate has long been regarded primarily as a safe flavor enhancer; however, contemporary experimental literature has drawn attention to its potential effects on the gut microbiome, metabolic profile, and functional state of the digestive tract. A systematic analysis of the literature suggests an association between monosodium glutamate consumption, alterations in gut microbial composition, and metabolic imbalance [1]. In a Wistar rat model, its administration was accompanied by changes in hepatic and renal metabolic profiles as well as in the composition of the gut microbiome [17]. It has also been established that dietary monosodium glutamate may increase visceral hypersensitivity, suggesting a possible functional effect on the gut–nervous system axis [8].

Ponceau 4R belongs to the group of synthetic azo dyes widely used to impart an appealing color to food products. The relevance of studying this compound is associated not only with its toxicological assessment but also with the need to monitor its actual concentration in food products. Contemporary analytical methods enable highly sensitive determination of Ponceau 4R in beverages and other food matrices [9, 15, 20]. Reviews addressing the safety of synthetic food colorants emphasize the need for further investigation of their potential effects on various body systems, including the digestive tract [4].

Another important area of contemporary research concerns the interaction between food additives and the gut microbiota. The gut microbiome is functionally linked to epithelial barrier integrity, nutrient metabolism, local immune responses, and systemic homeostasis. Alterations in its composition and metabolic activity may represent one of the central mechanisms through which food additives affect host health [13, 14, 21, 27, 28]. In this context, particular importance should be attached not only to the isolated effects of individual substances but also

to the possibility of a combined effect resulting from simultaneous exposure to several additives.

Such a model is the closest to real-world dietary exposure; however, it remains insufficiently investigated. A substantial proportion of experimental studies have examined individual additives, whereas studies of the combined E250, E621, and E124 exposure make it possible to assess morphological changes in the digestive system at different levels of organization, ranging from tissue and cellular remodeling to alterations in microcirculation and ultrastructure [5, 7, 12, 16, 18, 22, 30–32].

Of particular importance to contemporary morphological research are studies demonstrating remodeling of the duodenal wall, changes in villus parameters, alterations in the ultrastructure of the mucosa and submucosal glands, and disturbances of the exchange vessels of the microcirculatory bed [5, 12, 16, 18, 22, 30, 31]. Recent findings concerning the structural organization of the ileal mucosa under prolonged combined exposure further expand our understanding of the systemic nature of these abnormalities [19]. Thus, the accumulated experimental evidence requires an integrated analysis that takes into account current concepts of the interrelationship between morphological, metabolic, microbiota-related, inflammatory, and oxidative mechanisms.

An unresolved issue is whether the observed morphological changes can be regarded solely as consequences of the toxic effects of individual components or whether they reflect a complex interaction among food additives in which disruption of the intestinal barrier, gut dysbiosis, oxidative stress, microcirculatory disturbances, and alterations in the metabolic profile mutually reinforce one another. This issue underlies the relevance of the present analytical review.

The purpose of the study was to synthesize current experimental and analytical evidence concerning the morphofunctional effects of combined exposure to sodium nitrite, monosodium glutamate, and Ponceau 4R on the organs of the digestive system and to identify the principal mechanisms underlying the observed structural and functional abnormalities.

Materials and methods. The review was conducted as a structured analytical synthesis of scientific publications, following PRISMA reporting principles to ensure transparent reporting of the search, screening, and source-selection processes. The search strategy employed thematic combinations of key terms covering the substances and substance groups under investigation: «sodium nitrite», «monosodium glutamate», «Ponceau 4R», «food additives», «digestive system», «gastrointestinal tract», «gut microbiota», «intestinal mucosa», «liver», «salivary glands», «morphology», «ultrastructure», «oxidative stress», and «intestinal barrier», combined using relevant Boolean combinations.

Searches were conducted in the international bibliographic databases Scopus, Web of Science, PubMed/MEDLINE, EMBASE, and The Cochrane Library, supplemented by screening the reference lists of relevant review articles. Preference was given

to publications from the preceding five years; however, selected studies published in 2021 were retained as relevant experimental investigations contributing to the evidence base of the problem under consideration.

The inclusion criteria were: (1) studies investigating the effects of sodium nitrite, monosodium glutamate, Ponceau 4R, or their combinations; (2) assessment of structural, morphometric, ultrastructural, functional, metabolic, microbiota-related, or toxicological outcomes; (3) investigation of organs of the digestive system or processes directly related to digestive tract function; (4) availability of the full text or sufficient information for analytical assessment; and (5) publication in a peer-reviewed scientific journal.

Publications that did not concern the additives under investigation or the digestive system, duplicate records, reports lacking sufficient information on the effects studied, and sources that did not meet the established criteria of scientific relevance were excluded.

The selection process proceeded sequentially through identification of publications using the predefined keywords; removal of duplicate records; initial screening of titles and abstracts; assessment of full texts; verification of eligibility according to the inclusion criteria; and formation of the final evidence base. Following the final selection, 32 scientific publications were included in the analytical review, comprising systematic and narrative reviews and experimental *in vivo* studies.

Because the included studies differed substantially in experimental models, exposure duration, doses, organs examined, and outcome measures, a meta-analysis was not performed. Instead, a qualitative synthesis was undertaken, with findings thematically grouped into the following areas: gastric and intestinal changes; microcirculatory disturbances; hepatic and salivary gland injury; alterations in the gut microbiome; oxidative and inflammatory mechanisms; metabolic and functional consequences; and potential effects of combined exposure.

Results of the study and their discussion.

Analysis of the 32 selected publications demonstrated that the current evidence base concerning the problem under investigation is predominantly experimental. A substantial proportion of the studies were conducted in laboratory animals and focused on morphological, morphometric, and ultrastructural assessment of the digestive tract. At the same time, a parallel body of research has emerged addressing the interaction of food additives with the gut microbiome, metabolic processes, and intestinal barrier integrity [1, 13, 14, 21, 23, 27, 28].

A key finding of the analytical synthesis is the multilayered nature of the pathological effects. These effects do not involve a single anatomical structure but affect, either sequentially or concurrently, the mucosa, epithelium, villi, glandular components, microvascular bed, hepatic parenchyma, and salivary glands. This systemic pattern precludes viewing

combined exposure solely as a local effect on the intestine.

The consistency of the morphological findings with microbiome and metabolic-profile data is particularly noteworthy. Contemporary reviews indicate that food additives may alter the composition of the gut microbiota, disrupt the epithelial barrier, and affect metabolic homeostasis [14, 21, 27, 28]. At the same time, experimental models of combined exposure demonstrate that structural changes in the digestive tract may be sufficiently pronounced even in the absence of obvious clinical manifestations.

One of the most consistent areas of research concerns structural remodeling of the intestinal wall. In an experimental model of combined exposure to monosodium glutamate, sodium nitrite, and Ponceau 4R, remodeling of the duodenal wall was demonstrated [12]. These findings are of particular importance because the duodenum is the first segment of the small intestine to undergo intensive interaction with luminal contents after their passage from the stomach.

Detailed morphological assessment demonstrated alterations in the characteristics of the duodenal mucosal villi [32]. The villous apparatus accounts for a substantial proportion of the absorptive surface area of the small intestine; therefore, its structural remodeling may potentially affect membrane and luminal digestion, absorption, and epithelial interaction with the intestinal environment. Ultrastructural analysis confirmed that combined exposure was accompanied by changes at the subcellular level, indicating a more profound type of injury than isolated morphometric deviations [31].

Particular attention should be paid to the findings concerning the submucosal glands of the duodenum. One study demonstrated morphological changes in these glands under exposure to the combination of food additives [22]. Because glandular secretory activity is an important component of mucosal protection, structural alterations in these glands may represent a potential mechanism contributing to disruption of local homeostasis.

These findings are complemented by data concerning the stomach. An ultrastructural study of the fundic region of the rat stomach following exposure to the combination of food additives revealed alterations in the structural organization of its wall [30]. Thus, the pathological effects are not restricted to the small intestine but may develop as early as the upper regions of the digestive tract.

Recent findings concerning the ileum substantially broaden the understanding of the effects of combined exposure. Changes in the metric parameters of the ileal wall were identified following prolonged administration of the combination of chemical food additives [7]. A subsequent study of the structural organization of the ileal mucosa confirmed morphological remodeling of its components [19]. Thus, the distribution of changes along the digestive tract may indicate a systemic effect rather than a localized response of an individual intestinal segment.

Taken together, these findings suggest that prolonged combined exposure may create conditions conducive to disruption of the structural and functional integrity of the intestinal mucosa. The epithelial barrier, villous apparatus, glandular structures, and microvascular bed may be among the most vulnerable components.

The microvascular bed is a key functional component of the intestinal mucosa, ensuring the transport of oxygen and metabolites, maintaining epithelial energy balance, and contributing to the regulation of local inflammatory processes. Consequently, structural changes in the exchange vessels may have substantial functional consequences.

A study of the combined effects of monosodium glutamate, sodium nitrite, and Ponceau 4R demonstrated morphofunctional alterations in the exchange vessels of the ileal mucosa in the setting of nitrite accumulation [18]. Importantly, the vascular changes in that study were considered not in isolation but in the context of the combined exposure to three additives. This makes it possible to relate microcirculatory disturbances to other components of the pathological process, including alterations in the epithelium, mucosa, and tissue metabolism.

In parallel, evidence has been obtained of remodeling of the gingival microvascular bed under exposure to the combination of food additives [6]. Another study demonstrated changes in the morphological and functional parameters of the gingiva itself [5]. These findings broaden the concept of the systemic effects of food additives because the oral cavity represents the initial segment of the digestive tract, and its tissues come into direct contact with food components.

On this basis, a sequential morphofunctional pattern may be proposed: primary contact with food additives → alterations in local tissue homeostasis → microcirculatory disturbances → impaired trophic support and barrier function → progression of structural remodeling. This pattern requires further experimental validation but is consistent with findings obtained at different levels of organization.

The liver is a central organ of metabolism and biotransformation of numerous xenobiotics and therefore represents a target organ of particular importance for assessing the systemic toxicity of food additives. Experimental studies have demonstrated morphological changes in the hepatic parenchyma following administration of a combination of food additives [16].

Studies specifically addressing sodium nitrite have shown that its toxic effects are accompanied by disruption of redox balance, alterations in antioxidant defenses, and changes in inflammatory markers [2, 24]. At the same time, the protective effects of plant extracts in models of nitrite-induced hepatic injury further emphasize the role of oxidative stress in the pathogenesis of these changes [2, 10, 24].

Of particular interest are findings from a study of monosodium glutamate demonstrating simultaneous changes in hepatic and renal metabolic profiles and remodeling of the gut microbiome [17].

These findings suggest a possible interrelationship between intestinal and hepatic effects. Alterations in the microbiota may affect the profile of metabolites entering the portal circulation, while impaired hepatic function may, in turn, modify the metabolic environment of the intestine.

Accordingly, hepatic injury under combined exposure to food additives should be considered within the context of the gut–liver axis rather than as an independent toxic response of a single organ.

The oral cavity is the first anatomical component of the digestive system; however, it is often overlooked in studies of food additives. Available evidence indicates that combined exposure may affect gingival tissues and their microvascular component [5, 6].

Equally important are the findings concerning the salivary glands under conditions of nitrite-induced toxicity. Changes in the submandibular salivary gland and liver have been demonstrated in animals receiving sodium nitrite [3]. Another experimental study showed that this food additive may induce toxic changes in lung and salivary gland tissues associated with oxidative stress, inflammation, and fibrotic processes [11]. These findings are conceptually important because a food additive administered per os may affect different levels of the digestive system, from the oral cavity to the distal intestine and liver. Thus, the morphofunctional response of the organism is systemic in nature.

Among the three food additives investigated, sodium nitrite appears to have the most pronounced potential to contribute to the oxidative and inflammatory components of the toxic response. Experimental models demonstrate impaired antioxidant defenses and alterations in inflammatory markers in tissues following its administration [2, 11, 24]. This may be related to disruption of the balance between the generation of reactive oxygen species and the capacity of antioxidant systems to neutralize them. Persistent disruption of this balance creates conditions conducive to damage to membranes, proteins, nucleic acids, and intercellular structures. In the digestive tract, this may result in impaired epithelial barrier integrity and altered mucosal reactivity.

At the same time, an oversimplified interpretation should be avoided whereby all effects observed following combined exposure are automatically attributed to nitrite alone. The combined model involves substances with different biological properties, and the resulting effects may therefore reflect the cumulative contribution of several mechanisms.

Current evidence concerning monosodium glutamate indicates the need to move beyond an exclusively local approach to assessing its effects. A systematic review demonstrated an association between monosodium glutamate consumption, alterations in the gut microbiota, and metabolic dysbiosis [1]. In an experimental Wistar rat model, simultaneous changes in hepatic and renal metabolic profiles and the gut microbiome were observed [17]. These findings support consideration of monosodium

glutamate as a potential modifier of the «gut → microbiome → metabolism» axis. Alterations in microbial composition may be accompanied by changes in the production of short-chain fatty acids, amino acid metabolites, and other biologically active compounds. Disruption of microbial homeostasis may, in turn, affect epithelial barrier permeability and the local immune response.

An additional functional aspect is visceral hypersensitivity. Experimental evidence indicates that monosodium glutamate increases visceral sensitivity in a mouse model of pain [8]. Thus, morphological changes in the intestine may be accompanied by functional disturbances in its sensory regulation.

Ponceau 4R differs from sodium nitrite and monosodium glutamate primarily in its technological role as a synthetic colorant. Therefore, assessment of its potential biological effects should be complemented by evaluation of actual exposure levels. Current methods for determining Ponceau 4R in food products include high-performance liquid chromatography and spectrophotometric approaches [9, 15, 20]. The development of sensitive analytical methods is of fundamental importance for toxicological research because biological effects must be related not merely to the presence of the additive but also to its actual concentration and duration of exposure.

Reviews of synthetic food colorants emphasize that contemporary safety assessment should consider not only acute toxicity but also potential long-term effects associated with metabolism, inflammation, the microbiota, and intestinal barrier function [4]. In this context, Ponceau 4R assumes particular importance as a component of combined exposure.

One of the most promising contemporary concepts for explaining the systemic effects of food additives concerns their interaction with the gut microbiota. Recent reviews demonstrate that different classes of food additives may modify the bacterial composition of the intestine, alter microbial metabolites, and affect the epithelial barrier [13, 14, 21, 27, 28].

Of particular importance is the potential combination of microbiota alterations with inflammatory and metabolic disturbances. A systematic review by Singh et al. showed that food additives may be associated with dysbiosis, disruption of the intestinal barrier, and low-grade systemic inflammation, which are considered potential components of the pathogenesis of metabolic syndrome [23]. Other syntheses support the multifactorial nature of this process [14, 21, 27].

At the same time, an important methodological limitation should be emphasized: most contemporary microbiome studies concern individual classes of food additives or other substances rather than the specific combination of sodium nitrite, monosodium glutamate, and Ponceau 4R. Therefore, extrapolation of general patterns to this specific three-component exposure should be undertaken with caution.

Nevertheless, the available experimental evidence permits the hypothesis that combined exposure to these substances may operate according

to a “multiple-hit” principle: one group of components alters the redox balance, another modifies the metabolic and microbial environment, and a third may potentially affect the local tissue response. The resulting effect may be mutual amplification of disturbances in the barrier, secretory, trophic, and sensorimotor functions of the intestine.

Within the context of the present study, ultrastructural investigations are particularly valuable because they can reveal changes that may not yet be manifested at the level of overall tissue architecture. Studies of the duodenum and fundic region of the stomach have demonstrated ultrastructural remodeling under conditions of combined exposure [30, 31], which may indicate early disruption of cellular homeostasis preceding more pronounced tissue alterations. In the intestinal epithelium, particular importance should be attached to the condition of cell membranes, intercellular contacts, organelles involved in energy metabolism, and the secretory apparatus. Disturbances of these structures may potentially reduce barrier function and alter interactions between the mucosa and intestinal contents.

Accordingly, the most informative approach is to combine morphometric, histological, and ultrastructural methods when assessing the effects of food additives. Morphometric changes in the ileal wall [7] and alterations in the structural organization of its mucosa [19] are complemented by data on the vascular component [18], thereby enabling a more comprehensive morphofunctional interpretation.

On the basis of the analysis and synthesis of the available findings, a multilevel model of the interaction among sodium nitrite, monosodium glutamate, and Ponceau 4R may be proposed. The first level involves direct interaction between food components and food additives and the mucosal surfaces of the digestive tract; the second involves disruption of local redox balance and cellular homeostasis. For sodium nitrite, the role of oxidative and inflammatory mechanisms is most strongly supported [2, 11, 24]. In parallel, modification of the gut microbiome may occur. Contemporary reviews demonstrate that various food additives can alter microbial composition, microbial functional activity, and the intestinal metabolic profile [1, 13, 14, 21, 23, 27, 28]. The third level involves disruption of the epithelial and mucosal barriers. When barrier integrity is compromised, tissue exposure to bacterial components and metabolites may increase, potentially activating local inflammatory mechanisms. The fourth level is microcirculatory: structural and functional disturbances of the exchange vessels may impair mucosal trophic support and aggravate tissue hypoxia [18]. Similar alterations in the microvascular bed have been identified in oral tissues [6]. The fifth level comprises systemic metabolic effects. Findings concerning the liver demonstrate that the effects may extend beyond the intestine [16, 17]. Thus, the organs of the digestive system constitute a functionally interconnected system in which local disturbances may develop into a systemic response.

One of the most important unresolved issues is the nature of the interaction among the components of the combination. The mere presence of morphological changes following combined exposure does not establish synergism. Demonstration of a synergistic effect requires direct comparison of groups receiving each component separately, different two-component combinations, and the complete three-component combination at comparable doses and exposure durations.

Available evidence indicates that combined exposure may produce complex effects; however, quantitative discrimination among additive, potentiated, and synergistic effects remains insufficiently developed. Therefore, the results of morphological studies should be interpreted in the context of the experimental design.

Studies specifically evaluating the combination of sodium nitrite, monosodium glutamate, and Ponceau 4R are of particular value. They demonstrate simultaneous changes in different structural components of the digestive system, including the duodenal wall [12], intestinal villi [32], the fundic region of the stomach [30], the ileum [7, 19], mucosal vessels [18], the gingiva [5, 6], and submucosal glands [22]. The consistency of these findings supports the possibility of a systemic response to combined exposure.

Individual morphological studies acquire additional evidentiary value when considered in the context of contemporary reviews. Whelan et al. emphasized that food additives and ultra-processed foods may affect intestinal health through alterations in the microbiota, barrier mechanisms, and inflammatory processes [29]. Li et al. synthesized evidence concerning the effects of various food additives on the microbiome, intestinal barrier, metabolism, and systemic functions [14]. Wang et al. highlighted the central role of intestinal health in assessing the biological effects of food additives [28].

Recent findings by Seto et al. demonstrate that different classes of additives, including colorants, emulsifiers, sweeteners, and preservatives, may affect the mucus layer, epithelial barrier, microbiota, and local immune response [21]. This provides a broader context for interpreting the findings of studies of combined exposure. Accordingly, the morphological changes identified in experimental models should not be regarded as an isolated phenomenon. Rather, they are consistent with the contemporary concept of food-induced disruption of intestinal homeostasis, according to which mucosal structural integrity, the microbiota, metabolic processes, and immune regulation function as an interconnected system [13, 14, 21, 27, 28].

Despite the substantial amount of experimental evidence, the evidence base has several limitations. First, animal studies predominate, which limits direct extrapolation of the findings to humans. Second, experimental protocols differ in dosage, duration of administration, and exposure route. Third, individual studies focus on a single organ or morphological parameter, making systemic interpretation more difficult. Fourth, microbiome and morphological studies are often conducted using different experimental designs, which makes direct comparison of their findings methodologically challenging. Fifth, the specific three-component combination remains insufficiently investigated, whereas most international reviews consider food additives as a broad functional group [1, 14, 21, 23, 27].

At the same time, an important strength of the available evidence is the convergence of findings. Data from morphology, ultrastructure, morphometry, microcirculation, metabolomics, and microbiology do not contradict one another but instead provide a complementary picture. This convergence increases the biological plausibility of the hypothesis that combined exposure may produce effects at multiple interconnected levels.

Conclusion

Analysis of 32 scientific publications demonstrated that combined exposure to sodium nitrite, monosodium glutamate, and Ponceau 4R may be accompanied by complex morphofunctional remodeling of the digestive system involving the oral cavity, stomach, small intestine, liver, and salivary glands. Structural changes in the mucosa and wall of the duodenum and ileum, remodeling of intestinal villi and submucosal glands, ultrastructural alterations in the fundic region of the stomach, and changes in the exchange vessels of the mucosa have been demonstrated most consistently. The morphological abnormalities are consistent with evidence of alterations in the gut microbiome, metabolic profile, and functional activity of the digestive tract. Sodium nitrite may play a substantial role in the development of the oxidative and inflammatory component of injury, as supported by experimental data concerning the liver, salivary glands, and other organs. Evidence concerning monosodium glutamate suggests that it may affect the gut microbiota, metabolic homeostasis, and visceral sensitivity, thereby extending the traditional view of its biological effects. For Ponceau 4R, an important consideration remains the control of actual exposure levels, since assessment of its potential biological effects should take into account concentration, duration, and the combined nature of exposure. Taken together, current evidence supports consideration of the combined effects of food additives as a multifactorial process in which oxidative stress, inflammation, microcirculatory disturbances, dysbiosis, alterations in epithelial barrier integrity, and metabolic remodeling may interact. However, the available evidence is insufficient to establish definitively that the interaction among sodium nitrite, monosodium glutamate, and Ponceau 4R is synergistic. Standardized experimental studies directly comparing isolated, dual, and triple exposure are required.

Prospects for further research. Future research should focus on direct comparison of the isolated and combined effects of each component. A standardized experimental model should be developed that includes a control group; groups receiving sodium nitrite, monosodium glutamate, and Ponceau 4R separately; and groups receiving the respective two-component combinations and the three-component combination. Clinical studies should also be pursued, because findings from experimental models should not automatically be interpreted as evidence of clinically significant toxicity in humans.

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SEROUS DEMILUNES OF GIANNUZZI AND MORPHOFUNCTIONAL CHARACTERISTICS OF THE MAJOR SALIVARY GLANDS

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The salivary glands are key exocrine organs that maintain oral homeostasis, facilitate primary digestion, and provide immune defense. This review article summarizes historical and contemporary data on the morphology of the major salivary glands in humans and rodents, including the parotid, submandibular, and sublingual glands. Particular attention is focused on the serous demilunes of Giannuzzi, their morphological organization, cellular specialization, and secretory function. The study analyzes species-specific differences in the acini and ductal system, as well as the mechanisms of secretion for enzymes, mucins, and growth factors. The significance of historical research methods for the modern understanding of the morphofunctional organization of the glands and their clinical relevance is discussed.

Key words: salivary glands, serous demilunes of Giannuzzi, acini, ductal system, parotid gland, submandibular gland, sublingual gland.

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СЕРОЗНІ «ПІВМІСЯЦІ» ДЖІАННУЦЦІ ТА МОРФОФУНКЦІОНАЛЬНА
ХАРАКТЕРИСТИКА ВЕЛИКИХ СЛИННИХ ЗАЛОЗ**

Слинні залози є ключовими екзокринними органами, що забезпечують ротовий гомеостаз, первинне травлення та імунний захист. У цій оглядовій статті узагальнено історичні та сучасні дані про морфологію великих слинних залоз людини та гризунів, включаючи привушну, піднижньощелепну та під'язикову залози. Особлива увага приділена серозним «півмісяцям» Джіаннуцці, їхній морфологічній організації, клітинній спеціалізації та секреторній функції. Проаналізовано видові відмінності ацинусів та протокової системи, механізми секреції ферментів, муцину та факторів росту. Обговорено значення історичних методів дослідження для сучасного розуміння морфофункціональної організації залоз та їх клінічної значущості.

Ключові слова: слинні залози, серозні «півмісяці» Джіаннуцці, ацинуси, протокова система, привушна залоза, піднижньощелепна залоза, під'язикова залоза.

The study is a fragment of the research project "Systemic analysis of the morphological and functional state of various internal organs and body systems under the influence of irritants and mechanical injuries", state registration No. 0125U002785.

The salivary glands, as an anatomical and physiological structure, are key components of human oral homeostasis, as well as the digestive and immune systems. They facilitate the secretion of saliva, which is rich in enzymes, mucins, immunoglobulins, electrolytes, and biologically active substances. These components participate in

the initial processing of food, regulation of the microbiota, lubrication of the mucous membranes, and provision of antimicrobial defense [1, 5, 9]. These exocrine glands produce 0.5–1.5 litres of saliva every day, which, in turn, helps to facilitate chewing, swallowing and speech, lubricates the mucous membrane of the mouth and provides an aqueous