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The improvement of quaternary ammonium antiseptics for healthcare and dentistry needs. A review

Introduction. For a long time, quaternary ammonium compounds (QACs) have been the active ingredient of most antiseptics and disinfectants for healthcare and other sectors of economic activity. Surface-active QACs often combine disinfectant, wetting, foaming, and anticorrosive properties.

Aim of the work: to analyze available sources of scientific and medical information related to the development and application of quaternary ammonium compounds in healthcare and dentistry.

Materials and methods of the study. An information and patent search was conducted on the Internet on the websites of electronic libraries PubMed, MedLine, SciFinder, HEP Search, Jstor using the keywords "bi-quaternary ammoniums", "antiseptics", "antimicrobial agents", "ionic liquids" and "surfactants". The search depth was 10 years.

Research results and their discussion. In nature, QACS can be found in a number of plant alkaloids, terpenoids, acetylenes, coumarins, etc. Considering the isomerism and easy modification of QACS, their antimicrobial, toxic and surface-active properties can be successfully changed by essential modifications of the molecular structure – changing the number of charged nitrogen atoms (mono-, bis-, multi-QACS), changing the structure of the "head" of the molecule (non-heterocyclic, heterocyclic, aromatic), types of bonds (aliphatic, aromatic, saturated, unsaturated, mixed, etc.) and the structure of the "tails" (saturated, unsaturated, branched, unbranched), the properties are also dramatically affected by the length of the aliphatic chains. A separate type of QACS modification is the replacement of a substituent molecule. In addition to reducing the toxic and irritating properties of QACS (while maintaining their antimicrobial and virucidal properties), a separate promising way to improve them has become the synthesis of "hybrid" substances by forming their complexes with previously known antimicrobial agents. For example, the combination of QACS with semi-synthetic penicillins. A separate promising direction for improving the introduction of QACS into medical practice is the development of polymeric QACS and their salts as ionic liquids of a new type. And this has opened a whole new direction in the development of new antimicrobial agents of local action. The inclusion of QACS in the composition of dental composite filling materials reduces the risk of biodegradation of composites, which increases the durability of dental restorations and prevents the development of secondary dental caries. The caries-static effect is realized through bacteriostatic and anti-biofilm-forming effects. The improvement of dental composite technology consists in fixing the QACS themselves as low-functional groups on methacrylate monomers. Epoxy-functionalized QACS are new directions of development. These compounds are combined with epoxy resins, which can subsequently be polymerized. Such QACS can be included in the composition of polymers and retain a long-term bacteriostatic effect.

Conclusions: QACS are important substances for medical practice and dentistry in particular. The newest substances are promising antiseptics and antimicrobial agents that can be included in the composition of many types of medical devices. A progressive direction is the modification of epoxy resins and methacrylate monomers in dental composite materials by incorporating modified QACS into the structure.

Key words: quaternary amines, healthcare, dentistry, antiseptics, surfactants, composites.

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Удосконалення четвертинних амонієвих протимікробних засобів для потреб охорони здоров'я та стоматології. Огляд літератури

Вступ. Протягом тривалого часу четвертинні амонієві сполуки (ЧАС) виступають активною речовиною більшості антисептиків та дезсасобів для охорони здоров'я та інших галузей економічної діяльності. Поверхнево активні ЧАС часто поєднують в собі дезінфікуючі, змочувальні, піноутворюючі, антикорозійні властивості.

Мета роботи: проаналізувати доступні джерела науково-медичної інформації, яка стосується розвитку та застосування в охороні здоров'я та стоматології четвертинних амонієвих сполук.

Матеріали та методи дослідження – було проведено інформаційно-патентний пошук в мережі інтернет на сайтах електронних бібліотек PubMed, MedLine, SciFinder, HEP Search, Jstor за ключовими словами «бі-четвертинні амонії», «антисептики», «протимікробні засоби», «іонні рідини» та «поверхнево активні речовини». Глибина пошуку становила 10 років.

Результати досліджень та їх обговорення. У природі ЧАС можна знайти у складі ряду рослинних алкалоїдів, терпеноїдів, ацетиленів, кумаринів та ін. Враховуючи ізомерію та легку модифікацію ЧАС, їх протимікробні, токсичні та поверхнево активні властивості можуть бути успішно змінені шляхом основних модифікацій молекулярної структури – зміни числа заряджених атомів азоту (моно-, біс-, мульти-ЧАС), зміни структури «головки» молекули (негетероциклічна, гетероциклічна, ароматична), види зв'язків (аліфатичні, ароматичні, насичені, ненасичені, змішані та ін.) та структура «хвостів» (насичені, ненасичені, розгалужені, нерозгалужені), також на властивості різко впливає довжина аліфатичних ланцюгів. Окремий вид модифікації ЧАС це є заміна молекули-замісника. Окрім зниження токсичних та подразнювальних властивостей ЧАС (при збереженні їх протимікробних та вірулоцидних властивостей) окремим перспективним шляхом їх удосконалення став синтез «гібридних» речовин шляхом утворення їх комплексів із раніше відомими протимікробними засобами. Наприклад, комбінація ЧАС з напівсинтетичними пеніцилінами. Окремим перспективним напрямком удосконалення впровадження ЧАС у медичну практику є розробка полімерних ЧАС та їх солей, як іонних рідин нового типу. І це відкрило цілий новий напрямок у розробці нових протимікробних засобів місцевого впливу. Включення ЧАС до складу стоматологічних композитних пломбувальних матеріалів знижує ризик біодеградації композитів, що підвищує довговічність реставрацій зубів та перешкоджає розвитку вторинного карієсу зубів. Каріес-статичний ефект реалізується шляхом бактеріостатичним та протибіоплівкотворним ефектами. Удосконалення технології стоматологічних композитів полягає в фіксації самих ЧАС у якості малофункціональних груп на метакрилатні мономери. Епокси-функціоналізовані ЧАС є новими напрямками розвитку. Вказані сполуки з'єднують з епоксидними смолами, які в подальшому можуть бути полімеризовані. Такі ЧАС можуть бути просто включені до складу полімерів і зберігають тривалий бактеріостатичний вплив.

Висновки. ЧАС є важливими речовинами для медичної практики та стоматології зокрема. Новітні речовини є перспективними антисептиками та протимікробними засобами, які можна включати до складу багатьох видів медичних виробів. Прогресивним напрямком є модифікація епокидних смол та метакрилатних мономерів у стоматологічних композитних матеріалах шляхом включенням до структури модифікованих ЧАС.

Ключові слова: четвертинні аміни, охорона здоров'я, стоматологія, антисептики, поверхнево активні речовини, композити.

Introduction. For a long time, quaternary ammonium compounds (QACs) have been important components of most antiseptics and disinfectants, which are widely used in various sectors of the economy, from everyday life to healthcare, agriculture and industry. The period of anti-epidemic restrictions associated with the significant spread of diseases caused by SARS-COVID-19, 2020-2022, was marked by an increase in the frequency of use of QACs, which has already begun to affect specific ecosystems (as evidenced by the detection of QACs derivatives in dust samples and on work surfaces), and their concentration during pandemic processes doubled. Although the rationality of using QACs to prevent the spread of viral diseases is questionable, and such approaches require further research. The constant presence of subinhibitory concentrations of QACs in different ecotopes can lead to undirected selection of resistant microorganisms, which acts as an incentive for the synthesis and introduction into practice of new QACs that would exhibit antibacterial, antifungal and antiviral effects. Dental practice, as the most common type of medical care, also actively uses QACs. In general, QACs in the structure of the global market of antiseptics and antimicrobial agents occupy about 11% [1–7].

The purpose of the study is to analyze available sources of scientific and medical information related to the development and use of quaternary ammonium compounds in healthcare and dentistry.

Materials and methods of the study – an information and patent search was conducted on the Internet on the websites of electronic libraries PubMed, MedLine, SciFinder, HEP Search, Jstor using the keywords "bi-quaternary ammoniums", "antiseptics", "antimicrobial agents", "ionic liquids" and "surfactants". Review articles, results of clinical and experimental studies, critical discussions were selected. The search depth was 10 years.

Research results and their discussion

Structure and origin of quaternary ammonium compounds. Structurally, QACs consists of a positively

charged nitrogen atom, four (with four or three substituents) (Fig. 1).

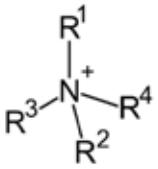

Fig. 1. Example of QACs structure

The main structure of QACs can contain one (mono-QACs), two (bis-QACs) or more (multi-QACs, poly-QACs) charged nitrogen atoms. It may be in heterocyclic compounds (piperidine, pyridine, imidazole, etc.). One or more substituents may be long aliphatic chains with at least 10 carbon atoms. The substituents are usually long aliphatic chains containing at least ten carbon atoms. The cationic cores of QACs are usually water-soluble and stable. The anions of the compounds usually do not affect their biological activity but often affect the solubility of QACs. The vast majority of registered QACs contain chloride or bromide as anions. Due to their amphiphilic nature, QACs are surface-active and capable of forming micelles. Surface-active QACs often combine disinfectant, wetting, foaming, and anti-corrosion properties. In nature, QACs and their homologs are components of several natural alkaloids, terpenoids, acetylenes, coumarins, etc. They can be found in some representatives of the plant world – *Gnetum montanum*, cinchona, tobacco, heart-shaped and small-fruited *Maclea*, etc. Such substances are: magnocurarine, latifolian, chelerythrine, berberine, ageloxime, tabouensinium chloride, quinocitrinines, sanguinarine, dehydroevodiamine, etc. [6, 7].

The first studies of QACs as an antimicrobial agent were carried out at the beginning of the 20th century. A prominent representative of such compounds was hexamethylenetetramine (urotropine), which showed a pronounced bactericidal effect in vitro. A big plus of the compound was its ability to decompose in the acidic environment of the kidneys and exocrine glands with the formation of pure formaldehyde, which already performs an antiseptic function. The next progressive significant step in introducing QACs into healthcare was the synthesis of benzalkonium chloride in 1935 in the laboratory of G. Domagk. Subsequently, several valuable properties of the specified mixture of substances for healthcare were discovered. Today, the benzalkonium chloride group is actively used as surfactants, personal hygiene products, cosmetics, softeners, dyes, biological dyes, and, of course, antiseptics and disinfectants of a broad spectrum of action [8–11].

In general, the simplicity of synthesis, enormous structural diversity and high biological activity have led to the active development of QACs research. Over the past 90 years, a large array of publications on the topic of QACs can be counted; for example, in 2020, more than 700 scientific articles were published on the properties of QACs. Considering the isomerism of QACs which also increases the variability of their effect, the antimicrobial, toxic and surface-active properties of QACs can be successfully changed by essential modifications of the molecular structure – changing the number of charged nitrogen atoms (mono-, bis-, multi-QACs), changing the structure of the "head" of the molecule (non-heterocyclic, heterocyclic, aromatic), types of bonds (aliphatic, aromatic, saturated, unsaturated, mixed, etc.) and the structure of the "tails" (saturated, unsaturated, branched, unbranched), the properties are also sharply affected by the length of the aliphatic chains. A separate type of QACs modification is the replacement of a substituent molecule. Therefore, during synthesis, it is possible quite significantly to change the main useful properties of QACs. That is, QACs are quite often modified in the direction of reducing their irritating and toxic effects [12–16].

Antimicrobial properties of some QACs. Benzalkonium chloride is a mixture of QACs with benzyl, methyl, and alkyl substituents with different chain lengths from C8 to C18. This drug was the first QACs to be officially approved for use in the USA back in 1947. The biological activity of benzalkonium salts depends on the length of the alkyl chain. It is known that C12–C14 compounds exhibit a more substantial bactericidal effect. Mostly, mixtures of benzalkonium salts have a broad spectrum of antimicrobial activity and a low level of toxicity. Therefore, they are widely used in detergents and disinfectants, rinse aids, cosmetics, cleaning agents, and household disinfection [1–3].

Benzalkonium salts have a bactericidal effect on staphylococci, streptococci, gram-negative bacteria (*Escherichia coli, Pseudomonas aeruginosa, Proteus, Klebsiella*, etc.), several anaerobic bacteria and fungi. They are also effective against strains of antibiotic-resistant bacteria and those resistant to some chemotherapeutic agents. Additional effects of benzalkonium are the inhibition of several powerful pathogenic factors of staphylococci – plasma coagulase and hyaluronidase. Also, benzalkonium chloride prevents secondary infection of wounds with nosocomial pathogens and can inactivate viruses. Derivatives of benzalkonium chloride include cetalkonium chloride (included in compositions for the treatment of lesions of the oral mucosa, also in ophthalmology). An example of a dental preparation is the gel "Cholisal" [17–20].

Further development of QACs technology led to the creation of the next generation of similar compounds – alkyl trimethylammonium bromides. The most famous of them are cetyltrimethylammonium bromide (CTAB) and dimethyldidecylammonium chloride (DDAC). The addition of a second long aliphatic chain in the structure of the amino compound increased the antimicrobial activity of the substance against S. aureus up to 8 times, but, at the same time, increased hematotoxicity [21, 22].

Miramistin (benzyldimethyl[3-(myristoylamino) propyl] ammonium chloride) is a non-heterocyclic alkyl cationic QACs, which was developed in the early 80s in the former USSR, and today is quite common in the countries of the former socialist camp. Miramistin is active against pathogenic fungi and viruses, demonstrating a moderate antiseptic effect. Its aqueous solutions are used in the treatment of purulent-inflammatory diseases in surgery, obstetrics, gynecology, dermatology, urology, dentistry,

and ophthalmology. Preparations containing Miramistin have a pronounced bactericidal effect on gram-positive (*Staphylococcus spp., Streptococcus spp., S. pneumoniae,* etc.), gram-negative bacteria (*Pseudomonas aeruginosa, Escherichia coli, Klebsiella spp.,* etc.), aerobic and anaerobic bacteria, both in the form of monocultures and microbial associations, including hospital strains that are multi-resistant to antibiotics. Antiviral effects on Hepadnaviruses and HIV have also been described [23, 24].

A separate direction in the development of antimicrobial QACs has become compounds based on pyridine. The simplest among them is ***cetylpyridinium chloride***. It was first synthesized and described shortly after the synthesis of benzalkonium – in 1939. Cetylpyridinium chloride has been widely used in oral care products and as a preservative in many types of products due to its pronounced bacteriostatic action. It acts as a cationic detergent. Quaternary ammonium compounds bind to the surface of bacterial cells, penetrate through it, and bind to the cytoplasmic membrane of the microorganism. As a result of binding, the cytoplasmic membrane of microbes increases the permeability of low-molecular ingredients, mainly potassium ions. The quaternary ammonium compounds then penetrate the cell, disrupting the functions of the cell and thus destroying it. Cetylpyridinium chloride has a broad spectrum of antimicrobial activity, as well as antifungal activity (e.g., against *Candida* and *Saccharomyces*) and antiviral activity against some enveloped viruses. The most pronounced is the bactericidal effect on gram-positive bacteria (in particular, *Staphylococci*). In vivo studies with cetylpyridinium chloride have demonstrated antiviral activity, but clinical relevance has not been determined. Gram-negative bacteria are moderately sensitive to cetylpyridinium chloride, while some strains of *Pseudomonas* are relatively insensitive [23, 25, 26].

Another typical representative of the pyridine subgroup of QACs is ***octenidine dihydrochloride***. Its dimeric structure is more complex than that of other typical substances of this class. Due to its molecular structure, it exhibits a broad spectrum of antibacterial activity, affecting *S. aureus, S. epidermidis, P. mirabilis, K. pneumoniae, E. coli, P. aeruginosa,* etc. Two cation-active centers, separated by a long aliphatic carbon chain, contribute to the binding of the molecule to negatively charged surfaces of microbial cells. Strong interactions between octenidine and lipids (in particular cardiolipins) in the membrane of bacterial cells are noted. Therefore, octenidine dihydrochloride has a deposition effect on human skin, and its traces can be detected even 24 hours after application. Therefore, due to its antimicrobial properties and skin compatibility, octenidine dihydrochloride can be used locally where a quick effect and long-term action are required. For example, for disinfecting the skin of patients or treating acute and chronic wounds spontaneously colonized or locally infected with pathogenic bacteria. Therefore, octenidine dihydrochloride can be used for the treatment of surgical equipment, processing the insertion site of central catheters, disinfection of root canals of teeth, and candidiasis, acne, and fungal nail infections [3, 4, 27, 28].

Decamethoxin is an antiseptic that also belongs to the QACs-group. Chemical name – 10-[dimethyl-[2-(5-methyl-2-propan-2-ylcyclohexyl)oxy-2-oxoethyl] azaniumyl]decyl-dimethyl-[2-(5-methyl-2-propan-2-ylcyclohexyl)oxy-2-oxoethyl]azanium;dichloride. Decamethoxin is a synthetic antiseptic and antifungal drug for topical use. The mechanism of action of the drug is to disrupt the permeability of the cytoplasmic membrane of bacteria and fungi by combining with the phosphatide groups of membrane lipids. The following pathogens are sensitive to decamethoxin: *staphylococci, streptococci*, *Corynebacterium spp., Stomatococcus spp., Pseudomonas aeruginosa, Candida spp., Microsporum spp., Trichophyton spp., Aspergillus spp., Penicillium spp., Giardia, Trichomonas*, the drug also has a virucidal effect. The drug inactivates diphtheria toxoid. There is no data on the absorption of decamethoxine from mucous membranes, intact skin, and wound surfaces, as well as on the systemic metabolism of the drug. Decamethoxine is used for local treatment of diseases of the oral cavity (stomatitis, ulcerative-necrotic gingivitis, dystrophic-inflammatory form of periodontitis of I–II degree in the acute stage), pharynx, larynx (with gingivitis, candidiasis of the oral mucosa, pharyngitis, laryngitis, tonsillitis); for sanitation of the oral cavity, pharynx, nasopharynx in carriers of pathogenic staphylococcus, diphtheria bacillus, candida; prevention of secondary infection after surgical interventions in the oral cavity, pharynx, larynx; locally also for the treatment of pustular bacterial and fungal skin diseases, microbial eczema, purulent-inflammatory lesions of soft tissues (abscesses, carbuncles, phlegmons, furuncles, purulent wounds, panaricium). It is also used endobronchially for lung abscess, bronchiectasis, cystic hypoplasia of the lungs complicated by suppuration, chronic bronchitis in the acute phase, and locally used for proctitis and ulcerative colitis. In ophthalmology, it is used in the form of eye drops for conjunctivitis and blepharoconjunctivitis and for the treatment of contact lenses. Decamethoxin is also used for the sterilization of medical instruments, devices, suture material, and rubber gloves and for chemical sterilization and preservation of bone and tendon transplants. Release forms – powder, tablets, eye drops, solutions [29, 30].

Ethonium is another synthetic antiseptic from the QACs group. The chemical name is ethylene-1,2-bis (dimethylaminodecyl acetate) dichloride. This compound was actively studied in scientific laboratories of Ukraine (Chernivtsi, 60-70s of the 20th century) as an antiseptic, and disinfectant drug. It has a bactericidal, bacteriostatic effect on both bacteria and fungi, and stimulates wound healing, tissue regeneration, and has a weak local anesthetic activity. Ethonium preparations are produced in Ukraine. It is used topically for the treatment of purulent wounds, burns of I-III-degree, trophic ulcers; rectal fissures, vaginitis; pyoderma, pruritic and infected dermatitis, dermatomycoses; stomatitis, gingivitis, periodontal diseases (application and instillation), for tooth filling (paste) [31, 32].

Sanguiritrin – is another representative of QACs. Chemically, it is a mixture of bisulfates of two quaternary benzophenanthridine alkaloids, sanguinarine, and chelerythrine, which are close in structure and properties. Sanguiritrin is obtained from the herb *Maclea cordata*

(Willd.) R.Br.) and *Maclea microcarpa (Maxim.)* Fedde) of the poppy family (*Papaveraceae*). Sanguiritrin has a wide spectrum of antimicrobial activity and acts on gram-positive and gram-negative bacteria, yeast-like and mycelial fungi. Active against antibiotic-resistant strains of microorganisms. In therapeutic doses, it acts bacteriostatically. The mechanism of the medicine's antimicrobial action is based on the inhibition of bacterial nuclease and disruption of the permeability processes of cell walls, division partitions, and nucleotide structure. Sanguiritrin is used as a prophylactic agent in newborns to prevent purulent-inflammatory skin diseases and in surgical patients to prevent wound infection. Sanguiritrin is used as a therapeutic agent: in infectious-inflammatory diseases of the skin and mucous membranes of bacterial and fungal etiology, including *Candida albicans*; in dentistry – in periodontitis, aphthous stomatitis, ulcerative-necrotic gingivostomatitis and other lesions of the oral mucosa; in otolaryngology – in angina, diseases of the middle ear and external auditory canal; in surgery – in infected burns, wounds that do not heal for a long time, and ulcers; in gynecology – for endocervicitis, colpitis, vaginitis, cervical erosion; in dermatology – for pyoderma, superficial blastomycosis, dermatomycosis [33, 34].

Modern directions of modification of QACs In addition to reducing the toxic and irritating properties of QACs (while maintaining their antimicrobial and virucidal properties), a promising way of their improvement was the synthesis of "hybrid" substances by forming their complexes with previously known antimicrobial agents. This option was the development of complex compounds in which the role of the anion was played by a semi-synthetic antibacterial agent from the penicillin group – ampicillin. This concept allowed to increase the water solubility of the complex drug and increase its antimicrobial effect. For example, the combination of ampicillin with cetylpyridinium or 1-hexadecyl-2,3-dimethylimidazolium increases the activity of the former against gram-positive and gram-negative bacteria, including even resistant strains. A separate promising direction for improving the introduction of QACs into medical practice is the development of polymeric QACs and their salts as ionic liquids of a new type. Moreover, this has opened a whole new direction in the development of new antimicrobial agents for local action [3, 4, 11, 35, 36].

A rather interesting direction has been the development of bactericidal coatings containing QACs, such as bioactive materials and antibacterial agents. Such products have already been brought to the level of industrial serial production. Antimicrobial films based on surface-modified microfibrillated cellulose with mono-QACs have antibacterial activity against *S. aureus* and *E. coli*, even at low concentrations. Silicon dioxide nanoparticles (silica), functionalized with lan QACs, inhibit the growth of gram-negative bacteria due to the synergistic effect of hydrophobicity and antibacterial activity. QACs with N-galamine coating on cotton fibers were active against *S. aureus* [3, 4, 37, 38].

Antimicrobial acrylic coatings with QACs-containing perfluoro-alkyl monomer with a light polymerization mechanism were synthesized. Polyvinyl-den fluoride membranes modified with QACs were developed, which have antibiofilm-forming properties. A separate direction of QACs development was bactericidal coatings containing ionic liquids. Such types of medical devices are among the most promising applications of ionic liquids in medicine and other industries. Ionic liquids are proposed to be used as components of ionogels, coatings, and membranes that demonstrate significant antimicrobial and antibiofilm-forming effects. Cellulose nanofibers with ionic liquids with QACs and silver ions deposited on the surface demonstrated pronounced antimicrobial activity against methicillin-resistant *S. aureus A* and *E. coli*. Technologies for hydrogel occlusive wound dressings with ionic liquids with QACs have been developed, which have a long-lasting antimicrobial effect against many pathogenic microorganisms [3, 4, 39, 40].

Modified polyvinyl-dene-fluoride materials with ionic liquids (1-vinyl-3-butylimidazolium chloride, 1-vinyl-3-ethylimidazolium tetrafluoroborate) showed activity against both common bacteria and "superbacteria". Calcium phosphate- with 1-alkyl-3-methylimidazolium chloride became a material with bactericidal properties, which was proposed for use in the production of intraosseous implants. A coating based on dication-imidazolium has been proposed for titanium implants, effectively inhibiting bacteria growth on titanium surfaces. In addition, 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide has been proposed as a bactericidal additive for dental cements for fixing orthopedic and orthodontic appliances, which reduced the level of bacterial biofilm formation [3, 4, 41].

QACs in the dental materials. QACs have long been used in many cosmetic products as preservatives and stabilizers. Therefore, such substances have been used for a similar purpose in the manufacture of dental materials, including fillings and sealers for the obturation of root canals. The inclusion of QACs in the composition of dental composite filling materials was motivated by the effect of reducing the level of biodegradation of dental composites under the influence of microorganisms in the oral cavity, which increases the durability of dental restorations and prevents the development of secondary dental caries. Such a caries-static effect is realized by disrupting the adhesion of microorganisms on the surface of dental polymers and reducing the rate of biofilm formation. The improvement of dental composite technology is not simply the inclusion of QACs in the composition of composite materials but in the fixation of QACs themselves as low-functional groups on methacrylate monomers. Such substances were dodecyl derivatives 66, which include sodium or ammonium lauryl sulfate, which is widespread in industry. Modified QACs dental polymers became powerful antimicrobial agents that, in the experiment, suppressed gram-positive and gram-negative bacteria and fungi, and the minimum inhibitory concentration was 0.8–25 μg/ml. Furthermore, the polymerization of the material itself slightly reduces the antimicrobial activity of the composite. Another QAC for such application was dimethylhexadecyl-methacryloxyethyl ammonium iodide, which can also be integrated into the structure of the methacrylate monomer. It has been shown that the inclusion of such a compound

in the composition of the composite effectively inhibits the growth of cariogenic streptococci and lactobacteria. Another development in this direction was the synthesis of a new QACs with a modified bromide counterion for inclusion in the methacrylate monomer, which allowed obtaining a compound capable of releasing fluoride ions during prolonged degradation. Such a monomer is biocompatible and inhibits the growth of *S. mutans* and *Lactobacillus casei*. A composite containing 3% of the above-mentioned modified substance demonstrates pronounced anti-biofilm-forming properties. However, in the development of the above-mentioned modified composite materials, there is an additional task – leveling the cytotoxic effect on the cells of the marginal periodontal tissue so as not to harm the viability of the former. Also, an important direction is to maintain the proper level of aesthetic and physical and mechanical properties of the modified composite materials. It is expected that the inclusion of QACs in the composition of dental composites will dramatically increase the caries-static properties of dental filling materials [42–45].

Epoxy-functionalized QACs are new directions in the development of compounds. Representatives of this subgroup are derivatives of dodecyl and tetradecyltrimethylammonium with modifications by organic acids. These compounds are combined with epoxy resins, which can be further polymerized. Such QACscan be simply included in the composition of polymers and retain bacteriostatic properties. iv. Researchers from different countries have gained experience in modifying dental sealers with such QACs as benzalkonium chloride and cetylpyridinium chloride. For example, Arias-Moliz et al. demonstrated the antibacterial properties of the AH Plus ™ root canal sealer, which included benzalkonium chloride. The material causes a pronounced bacteriostatic effect on *Enterococcus faecalis* [42, 2, 3, 4, 46–48].

Conclusions. Therefore, for a long time now, quaternary ammonium compounds (QACs) have been the active ingredient of most antiseptics and disinfectants for healthcare and other industries. Surface-active QACs often combine disinfectant, wetting, foaming, and anticorrosive properties. In nature, they can be found in several plant alkaloids, terpenoids, acetylenes, coumarins, etc. Considering the isomerism and easy modification of QACs, their antimicrobial, toxic and surface-active properties can be successfully changed by essential modifications of the molecular structure – changing the number of charged nitrogen atoms (mono-, bis-, multi-QACs), changing the structure of the "head" of the molecule (non-heterocyclic, heterocyclic, aromatic), types of bonds (aliphatic, aromatic, saturated, unsaturated, mixed, etc.) and the structure of the "tails" (saturated, unsaturated, branched, unbranched), the length of the aliphatic chains also dramatically affects the properties. A separate type of QACs modification is the replacement of a substituent molecule. Therefore, during synthesis, it is possible to change the main beneficial properties of QACs significantly. That is, QACs are quite often modified in the direction of reducing their irritating and toxic effects. In addition to reducing the toxic and irritating properties of QACs (while maintaining their antimicrobial and virucidal properties), a separate promising way to improve them has become the synthesis of "hybrid" substances by forming their complexes with previously known antimicrobial agents. For example, the combination of QACs with semi-synthetic penicillins. A promising direction for improving the introduction of QACs into medical practice is the development of polymeric QACs and their salts, as ionic liquids of a new type. And this has opened a whole new direction in the development of new antimicrobial agents for local action.

Including QACs in the composition of dental composite filling materials reduces the risk of biodegradation of composites, which increases the durability of dental restorations and prevents the development of secondary dental caries. The caries-static effect is realized through bacteriostatic and antibiofilm-forming effects. The improvement of dental composite technology consists in fixing the QACs themselves as low-functional groups on methacrylate monomers. Epoxy-functionalized QACs are new directions in the development of QACs. Representatives of this subgroup are dodecyl and tetradecyltrimethylammonium derivatives with modifications by organic acids. These compounds are combined with epoxy resins, which can subsequently be polymerized. Such QACs can be included in the composition of polymers and retain a long-term bacteriostatic effect.

QACs are important substances for medical practice and dentistry in particular. The newest substances are promising antiseptics and antimicrobial agents that can be included in the composition of many types of medical devices. A progressive direction is the modification of epoxy resins and methacrylate monomers in dental composite materials by including modified QACs in the structure.

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