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ANTIMICROBIAL POTENTIAL OF IODINE-CONTAINING SUBSTANCES AND MATERIALS

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ABSTRACT

Despite the search and development of new antimicrobial drugs with antibiotic or antiseptic properties, the spread of multidrug-resistant strains of microorganisms remains a serious problem in the treatment and prevention of infectious diseases (wound, postoperative and burn infections, preoperative preparation of the surgical and injection fields, hygienic disinfection of the hands of surgeons, medical personnel, etc.). This review of modern domestic and foreign literature sources is devoted to the analysis of data on the prospects of using antiseptics with iodine and iodides as antimicrobial agents. In modern conditions, there is an increasing number of scientific works devoted to the study and development of various drugs, distinguished by their diversity and their specific application. Antimicrobial iodine-containing compounds can be applied to a wide range of materials such as textile, plastics, metals, ceramics to make them resistant to microbial and biofilm growth. The article summarized the literature data on the high antimicrobial activity of iodine both in neutral carriers and in synergy with substances already possessing similar properties. Such complex preparations lose their toxicity to a large extent, having prolonged action with the preservation of their properties. The main mechanisms of antimicrobial action of iodine and iodine compounds are determined by their strong oxidizing ability. Attention is drawn to the spectrum of activity of iodine preparations. Along with the antimicrobial effect, they can promote regeneration processes. In general, innovative iodine preparations with antibacterial and fungicidal properties are promising for medical and other purposes.

Key words: *iodine, iodine preparations, practical use, antimicrobial activity, opportunistic microorganisms*

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АНТИМИКРОБНЫЙ ПОТЕНЦИАЛ ЙОДСОДЕРЖАЩИХ ВЕЩЕСТВ И МАТЕРИАЛОВ

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РЕЗЮМЕ

Несмотря на поиск и разработку новых антимикробных препаратов с антибиотическими или антисептическими свойствами, распространение полирезистентных штаммов микроорганизмов по-прежнему остаётся серьёзной проблемой в лечении и профилактике инфекционных заболеваний (раневые, послеоперационные и ожоговые инфекции, предоперационная обработка операционного и инъекционного поля пациента, гигиеническая обработка рук хирургов, медицинского персонала и т. д.). Настоящий обзор современных отечественных и зарубежных литературных источников посвящён анализу данных о перспективах применения веществ и материалов с йодом и йодидами в качестве антимикробных агентов. В современных условиях возрастающее количество научных работ посвящены изучению и разработке различных препаратов, обладающих характеристиками, специфичными для их применения. Антимикробные соединения с йодом могут быть применены к широкому спектру материалов, таких как текстиль, пластик, металлы, керамика, что позволяет этим материалам быть устойчивыми к микробному росту и росту биоплёнок. Обобщены литературные данные по высокой антимикробной активности йода как в нейтральных носителях, так и в синергии с уже обладающими подобными свойствами веществами. Такие комплексные препараты в значительной мере теряют токсичность, действуя пролонгировано с сохранением своих свойств. Основные механизмы противомикробного воздействия йода и соединений с йодом предопределяет их сильная окислительная способность. Обращено внимание на спектр активности препаратов йода. Наряду с антимикробным эффектом, они могут способствовать процессам регенерации. В целом инновационные препараты с йодом с антибактериальными и фунгицидными свойствами перспективны для медицинских и других целей.

Ключевые слова: *йод, препараты йода, практическое использование, антимикробная активность, условно-патогенные микроорганизмы*

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INTRODUCTION

The treatment of diseases caused by infections is currently complicated by the diversity of strains and the emergence of microbial resistance to preparations such as antiseptics and antibiotics [1]. For instance, some microorganisms showed decreased sensitivity to chlorhexidine, triclosan, peracetic acid, benzalkonium chloride, mupirocin, tetracycline and others. [2–4]. The increase in antimicrobial resistance has currently led to fewer treatment options for patients and an associated increase in morbidity and mortality. According to the World Health Organization (WHO), antimicrobial resistance is a global threat to human health and development, and the overuse of these preparations is a major factor in the growth of drug-resistant strains [5].

Susceptibility and resistance to antiseptics and antibiotics are caused by natural adaptive mechanisms regulated by chromosomal DNA as well as by extra-chromosomal elements (plasmids, transposons, etc.) that can move within the genome throughout a single cell or be transmitted to other members of the community through horizontal gene transfer. Phenotypic and genetic mechanisms of antimicrobial resistance have been identified, with the main ones being restriction of drug transport through the cell wall, modification of the drug target, drug deactivation and active drug excretion by outflow systems, as well as the biofilm formation [6].

In about 80 % of chronic and recurrent bacterial infections in the human body are considered to be associated with the biofilm structures formed by infectious agents [7]. Biofilms represent microbial cells in an extracellular matrix produced by them, consisting of polysaccharides, extracellular DNA and other components. As compared to planktonic cells, cells in biofilm are much less sensitive to antimicrobials and this becomes a major cause of ineffective treatment. New technologies development in medicine leads to the expansion of the range of creation and application of various materials, including those with antimicrobial properties, antimicrobial agents of bactericidal and bacteriostatic action of local and systemic application. An important place among modern antiseptic agents, which are an integral part of medicine, is currently being occupied by iodine preparations.

Iodine is known to have antimicrobial activity against a wide range of microbial strains. Being widespread in nature, performing a variety of functions within the majority of living organisms, relatively low cost and environmental safety, iodine has a high potential for use as an antimicrobial agent. Microbial resistance to iodine has not been identified to date. It has recently been shown by the example of *Staphylococcus aureus* that even subinhibitory concentrations of povidone iodine do not lead to the emergence of iodine-resistant bacterial strains [8]. It is caused by the wide variety of microbial cell targets damaged by iodine. The effective disinfection time of bacterial cell populations has been revealed to be between 3 and 15 s at concentrations ranging from 6 to 13 ppm of available iodine, although spores were found to be more resistant to iodine compared to vegetative cells [9]. The elemental iodine, however, is toxic and volatile and can be destroyed by ultraviolet rays, making it difficult to use. Additionally, since iodine is an active oxidant, its partial inactivation by proteins is possible during *in vivo* contact with internal tissues. Consequently, safe materials and preparations containing iodine compounds with certain characteristics that favour the use of iodine regardless of environmental factors are still being developed. An opportunity to obtain stable forms with iodine expands its application as an antiseptic in various spheres, including medicine, veterinary medicine, food industry.

With reference to the above, the aim of the current review is to substantiate the efficacy of iodine, iodine compounds and iodine-containing complexes against infectious agents and to characterize their antimicrobial activity.

CHARACTERISTICS OF IODINE

Iodine, along with chlorine, is a halogen often used to kill microorganisms. The name had come from the Greek "iodes", which means "purple". Iodine is widely, albeit in very diverse concentrations, distributed in nature. It is mainly found in the marine environment. In nature, iodine is known to be involved in the metabolism of some microorganisms. Bacteria can both oxidize and methylate iodide and can also accumulate iodide [10]. Iodine in human biology regulates metabolism, affects the immune and antioxidant systems [11].

Halogens appear to be strong oxidizing agents since they have seven electrons on their outer shell; as oxidizing agents, halogens accept an electron, becoming a halide ion. The antimicrobial efficacy of halogens is a result of both their oxidative capacity and substitution reactions. Halenes, however, differ in their oxidizing potential and disinfecting ability. In particular, the halogen with the strongest oxidizing capacity is fluorine, followed by chlorine, bromine and iodine [12]. However, among these halogens, iodine is the more stable element in the environment.

Iodine is poorly soluble in water; it has been reported that the biological effects of this halogen are associated with its relative hydrophobicity [13]. Iodine has also been reported to be lipophilic and this favours its diffusion through the cell membrane of microorganisms [14]. The water solubility of iodine can be increased in the presence of iodide ions, where polyiodide formation occurs; in order to do this, potassium iodide is most often added to the solution [15]. Although iodine is much better soluble in alcohols, these solvents penetrate the tissues too quickly, causing an excess of iodine, which in turn leads to irritation and other undesirable side effects [16]. A number of studies are available examining the cytotoxicity of iodine and its complexes on fibroblasts, keratinocytes and other cell lines [17].

Some evidence exists demonstrating that compounds containing chlorine and iodine are equally effective in killing vegetative cells, but chlorine compounds are more effective in inactivating spores [9].

Many studies have repeatedly confirmed that elemental iodine I_2 is the most powerful antimicrobial agent compared to other forms of iodine. It is followed by hypoiodous acid (HIO) [18] and the iodine cation H_2OI^+; other forms of iodine dissolved in water have no bactericidal activity [19].

MECHANISMS OF IODINE ANTIMICROBIAL ACTIVITY

Being a small molecule, iodine is able to penetrate the cell wall of microorganisms and react with various cellular components such as proteins, nucleic acids and lipids. As a result, proteins are denatured, nucleic acids are oxidized and cell membranes are destroyed, ultimately leading to cell death. Aromatic hydrocarbons, sulfur-containing amino acids (cysteine, methionine) and unsaturated fatty acids appear to be the main targets [20]. Protein denaturation is achieved by oxidation of SH-groups in cysteine and methionine, and the formation of hydrogen bonds between the amino groups of arginine and histidine and the phenolic groups of tyrosine is also prevented. Iodine is capable of binding to fatty acids via carbon-carbon bonds and to some nucleotides (adenine, cytosine and guanine), thereby changing the structure of nucleic acids, causing DNA strand breaks and mutations in genetic material [21]. Iodine is also effective in inhibiting the activity of enzymes involved in the metabolic pathways of microbes. Eukaryotes are using the reactivity of some iodine species to counteract infections. In mammals, antimicrobial forms of iodine can be secreted as by-products of peroxidases [11]. It induces oxidative stress and eventually leads to microbial cell death. In summary, the antimicrobial mechanism of iodine involves several nonspecific pathways targeting different components of microbial cells, making it an effective and versatile antimicrobial agent.

IODINE PREPARATIONS ACTIVITY SPECTRUM

It is one of the few antimicrobial agents that had been found to be effective against bacteria, viruses, fungi and protozoa as a consequence of its oxidizing properties. *Candida* species are resistant to many antifungal agents. They are capable of producing biofilm, which is an important factor in the pathogenesis of candida infections [22]. It has been also demonstrated that iodine has strong antifungal activity against *Candida* species, including *Candida albicans*, and inhibits the growth and formation of their biofilms. Iodine preparations are known to induce oxidative stress in *Candida* cells. However, there are strains that are less susceptible to oxidative stress. Thus, a study by S. Cuellar-Rufino et al. have revealed mutant strains producing catalase and superoxide dismutases 1 and 2 among *Candida glabrata* strains, which appeared to be more resistant to iodine [23]. Iodine preparations also have fungicidal activity against other genera, including *Aspergillus* [24].

It is considered that the thicker the peptidoglycan layer, the more resistant bacteria are to surfactant antimicrobial preparations [25]. Obviously, iodine preparations have a different effect on the cell membrane of gram-positive and gram-negative bacteria as a result of their structure peculiarities. Gram-positive bacteria have no outer membrane, however, this is compensated for by the construction of a thicker cell wall with peptidoglycan [25]. Peptidoglycan consists of polymerized glycans that form linear chains cross-linked by short peptides. These glycan filaments consist of β-1,4-bound N-acetylglucosamine residues alternating with N-acetylmuramic acid residues [26]. Since iodine is a highly reactive oxidant, there is probably an ability to break chemical bonds in the peptidoglycan layer. Gram-negative bacteria are generally being more protected since their outer membrane, which acts as a permeability barrier for various substances, can probably make iodine penetration less efficient as well [27]. Iodine inactivation of outflow pumps is an important issue, since many multiple drug resistance strains have pumps to remove toxic compounds from the periplasm and cytoplasm [28]. Iodine has the potential to induce the production of reactive oxygen species [29], and in a study of the effects of singlet oxygen on gram-positive and gram-negative bacterial strains, it was revealed that the gram-negative *Escherichia coli* strain was less sensitive to oxidative stress due to the outer membrane compared to the gram-positive *Enterococcus faecium* strain [30].

ANTISEPTIC PREPARATIONS AND MATERIALS WITH IODINE

Since the anti-septic properties of iodine have been discovered, many different preparations with iodine as an active ingredient have been developed. I.V. Popov et al. differentiate the history of creation of these antiseptics into two stages: before the middle of the 20th century – simple; after the middle of the 20th century – complex iodine-containing antiseptics [31]. The authors emphasize in their review that both iodophores and iodine-containing antiseptics derived from enzyme systems and their modifications are currently available for use in practice.

Existing iodine preparations and remedies are diverse in form, including alcoholic 5 % iodine solution, iodized solutions, iodized films and dressings, ointments and creams containing iodine, as well as in properties and areas of application (medicine, veterinary medicine, ecology, food industry). Common combinations with iodine that may be contained in antiseptics include iodine and alcohol, aqueous iodine solution, iodine and polyvinylpyrrolidone, iodine and polyvinyl alcohol, iodine and formaldehyde, and others. Each of the iodine-based antiseptics available on the market today has its own features and recommendations for use.

Antiseptic preparations based on molecular iodine are called iodophores. They are applied in the prevention and in the treatment of infectious complications in medicine and veterinary medicine. The most widely used of the lat-

ter has been povidone iodine available for more than sixty years. This iodophor remains a highly effective agent for the treatment of acute and chronic wounds as a result of its rapid, potent antimicrobial action on both planktonic cells and biofilms [32]. Free iodine is slowly being released from the complex, thereby allowing the gradual release of small amounts of iodine that are not toxic to tissue cells. Forms of povidone iodine preparations are diverse, in various concentrations – from 9 to 12 % – it is available in the form of solution, spray, ointment, etc. [19]. Comparison of 5 % povidone iodine solution with 1 % *in vitro* revealed greater efficacy at lower concentration [33]. Native povidone iodine is hydrophilic, has a pH of about 4.0 and may have an irritant effect [33, 34]. Its antibacterial activity is observed in the pH range of 2.5–7.0 [21]. It has low cytotoxicity compared to many other antiseptics [35]. However, there is evidence that povidone iodine may have cytotoxic effects on human and animal tissue cells, negatively affecting wound healing in preclinical trials, especially in early stages [17]; an increased risk of sensitization has also been reported [36]. Therefore, the search for new iodophores is relevant, as evidenced by the analysis of the literature in recent years.

In addition to povidone iodine, there are many compounds with iodine. Complexation can contribute to controlled release (polymers can be designed for slow and stable release of iodine, which provides a stable antimicrobial effect without cytotoxic effect), increased stability (since iodine can be unstable and easily decompose, but when encapsulated in a matrix it can be protected from decomposition and maintain its antimicrobial activity for long periods time), improved adhesion (the ability to adhere to surfaces such as skin or a water purification filter), reduced toxicity (by minimizing contact of high concentrations with human cells and tissues). These complexes contain molecular iodine, iodide ions, and polymeric substances. Iodine complexes are usually produced hydrophobic as they interact more easily with the bacterial membrane, which consists of a double lipid layer. The hydrophobic material is also better at adsorbing proteins than the hydrophilic material [37]. A significant parameter for a drug has been its surface potential (zeta potential) as it affects its ability to attach to other surfaces as well as to cells.

Iodine carrier polymers may be both of natural (chitosan, chitin, albumin, starch, glycogen, silk, etc.) and synthetic origin (polyvinyl alcohol, polyvinylpyrrolidone, polyamides, etc.) [15]. Apart from that, there are binary compounds of iodine with metals that mutually enhance bactericidal properties of each other. The antibacterial and fungicidal activities of some substances and materials with iodine are summarized in Table 1.

Recently, cationic acrylate copolyvidone-iodine nanoparticles (CACPVI) have been obtained [38]. Being positively charged on its surface, CACPVI demonstrated excellent antibacterial effects on *E. coli*, since the phospholipid molecular layer on the cell membrane of gram-negative bacteria is negatively charged, and inhibited *S. aureus* at a slightly higher concentration. This antibacterial polymer material has a long-lasting effect and is capable of finding applications in the creation of coatings, dyes and inks to minimize bacterial infection.

Iodophor based on antimicrobial rubber nanocapsules of trans-polyisoprene (TPI) has been not only proven to have antimicrobial effects but also promotes wound healing [17]. It was found that this iodophore had the properties of amphiphilicity and biocompatibility, as well as the ability to stimulate cell proliferation. In the study, iodophor was compared with the clinical drug povidone-iodine and demonstrated better antibacterial activity on *E. coli*.

Z. Edis et al. obtained the triiodide complex $[Na(12\text{-crown-}4)_2]I_3$ [14]. Triiodide complex proved to be a broad-spectrum bactericidal agent against reference and clinical isolates of gram-positive *(Streptococcus pneumoniae*, *S. aureus*, *Enterococcus faecalis*, *Streptococcus pyogenes*, *Bacillus subtilis*), gram-negative bacteria *(Proteus mirabilis*, *Klebsiella pneumoniae*, *E. coli*, *Pseudomonas aeruginosa*) and *C. albicans*. Although the size and molecular weight prevent the passage of this compound through the membrane of a bacterial cell, $[Na(12\text{-crown-}4)_2]I_3$ is attracted to it through electrostatic interactions. This compound is hydrophobic and lipophilic, which presumably enhanced the antimicrobial activity. The strong halogen bond between the triiodide ions, however, prevented the release of free molecular iodine. As a result of this phenomenon, on the other hand, the compound $[Na(12\text{-crown-}4)_2]I_3$ remains stable for a long time.

L. Tonoyan et al. have announced the synthesis of a biocidal complex, which is formed following the reaction between ion-oxidisable salts iodide and thiocyanate in the presence of hydrogen peroxide as an oxidation source [39]. Iodine-thiocyanate complex (ITC) is able to incorporate more molecular iodine than povidone iodine. The sensitivity of *E. coli* ATCC 25922, *P. aeruginosa* NCIMB 10421, *S. aureus* DSM 15676 and *S. aureus* MRSA BH1CC strains, their single-species biofilms, as well as two-species biofilms of *S. aureus* DSM 15676 and *Streptococcus uberis* strains were tested to ITC. ITC demonstrated antimicrobial activity against all strains and biofilms tested. The minimum bactericidal concentrations and the minimum concentrations for the destruction of biofilm were in the range of 7.8–31.3 and 31.3–250 $\mu g \times mL^{-1}$, respectively. Against *P. aeruginosa* biofilm, ITC was considered by the authors as the least effective, as a concentration of 125 $\mu g \times mL^{-1}$ was not sufficient for complete killing, but a significant reduction in cell number was observed. The minimum eradication concentration of the mixed biofilm was 250 $\mu g \times mL^{-1}$. This complex can be applied as an antimicrobial agent and for surface disinfection. Further biocompatibility studies are needed.

The hemostatic macroporous polymer foams developed by J.G. Lundin et al. were found to be capable of smooth sustained iodine release as a result of high iodine loading, whereas low loading resulted in its abrupt release [40]. The kaolin contained in the complex served as a haemostatic agent and influenced iodine content and its release rate. In combination with iodine, these polymers are active against *E. coli, K. pneumoniae, P. aeruginosa* and *S. aureus*. This development can be used as a dressing material for wounds.

TABLE 1

IODINE-CONTAINING SUBSTANCES AND MATERIALS AND THEIR ANTIBACTERIAL AND FUNGICIDAL EFFECTS

Names of substances and materials with iodine/ iodides	The substance under study	Strains	Antibacterial and fungicidal effects	Reference
CACPVI	Nanoparticles of about 200 nm in size	*E. coli*, *S. aureus*	Completely inhibited the growth of *E. coli* at a concentration of 20.00 μg × mL^{-1}. Inhibited the growth of *S. aureus* at a concentration of 40.00 μg × mL^{-1}.	[38]
Trans-polyisoprene rubber nanocapsules doped with iodine for 9h (TPI NPs-I_2-9h) and 24h (TPI NPs-I_2-9h)	Spherical rubber nanoparticles with an average diameter of ≈ 120 nm	*E. coli*	Iodide concentration: TPI NPs-I_2-9h, 1.5 wt%; TPI NPs-I_2-24h, 2.5 wt%. MIC: TPI NPs-I_2-9h – 2.5 μg/mL; TPI NPs-I_2-24h – 1.25 μg/mL;	[17]
Triiodide complex [Na (12-crown-4)$_2$]I_3	Lipophilic complex in the form of triclinic crystals	Reference and clinical strains of *S. pneumoniae*, *S. aureus*, *S. pyogenes*, *E. faecalis*, *B. subtilis*, *P. aeruginosa*, *E. coli*, *K. pneumoniae*, *C. albicans* species	The complex at a concentration of 13.3 mg/mL showed ZOI: *S. aureus* – 43 mm, *S. pyogenes* – 34 mm, *E. faecalis* – 39 mm, *S. pneumoniae* – 28 mm. ZOI for *B. subtilis* is 15 mm. At a concentration of 10 mg/mL, the ZOI was: *E. coli* – 23 mm, *P. aeruginosa* – 20 mm, *K. pneumoniae* – 15 mm. ZOI of a clinical sample of *C. albicans* was 50 mm at a concentration of 13.3 mg/mL. ZOI for *C. albicans* WDCM 00054 – 40 mm at a concentration of 10 mg/mL.	[14]
Iodine-thiocyanate complex (ITC) (H_2O_2/KI/KSCN)	A solution of H_2O_2/ KI/KSCN in a ratio of 1:1:1 with a 1% final concentration of the components	*E. coli* ATCC 25922, *P. aeruginosa* NCIMB 10421, *S. aureus* DSM 15676, *S. aureus* BH1CC	MIC/MBC (μg × mL^{-1}): *E. coli* – 15.6/15.6; *P. aeruginosa* – 31.3/31.3; *S. aureus* – 7.8/7.8; *S. aureus* – 15.6/15.6	[39]
Hemostatic macroporous polymeric polyethylene glycol polymer foams enriched with iodine in the form of triiodides	Polymer foam with macroporous structure	*E. coli* ATCC 35695, *S. aureus* ATCC 11987, *K. pneumoniae* ATCC 13883, *P. aeruginosa* ATCC 27853	The ZOI for *E. coli* was 14 ± 1 and 22 ± 2.7 mm; for *K. pneumoniae* – 9.2 ± 0.3 and 19.33 ± 3.2 mm; for *S. aureus* – 12.8 ± 0.3 and 27.8 ± 2.5 mm with KFoam-0.1 and KFoam-1.0 respectively; for *P. aeruginosa* – 14.7 ± 2.1 with KFoam-1.0.	[40]

Note. CACPVI – cationic acrylate copolyvidone-iodine nanoparticles; TPI – trans-polyisoprene; MIC – minimum inhibitory concentration; [Na(12-crown-4)$_2$]I_3 – sandwich complex of two 12-crown-4 molecules surrounding one sodium ion; ZOI – inhibition zone; ITC – iodine-thiocyanate complex; H_2O_2/KSCN – hydrogen peroxide in combination with potassium thiocyanate; MBC –minimum bactericidal concentration; KFoam-0.1, KFoam-1.0 – samples of polymer foam with kaolin impregnated with iodine solutions in ethanol in 0.1 % and 1.0 % mass ratios, respectively.

An assessment of the antimicrobial activity of polyazolidinediammonium modified iodine hydrate ions (PAAG-M) has demonstrated antibiofilm activity against the type strain of *E. coli* ATCC 25922 and clinical *E. coli* FimH [41]. High-

er sensitivity was observed in *E. coli* carrying the virulence gene *FimH*. The complex was previously evaluated against reference strains and clinical isolates of bacteria, microscopic fungi, and RNA-containing viruses [42]. The preparation was found to have an efficient bactericidal effect against strains of gram-positive (*S. aureus* 209P, *Bacillus cereus* 8035) and gram-negative bacteria (*E. coli* 113 – 13, *P. aeruginosa* ATCC 27853), with gram-positive bacteria being more sensitive to this complex [43]. With these findings, PAAG-M should be recommended for use in the treatment of medical devices to prevent infections, including those associated with the presence of microbial biofilms.

As far back as in the last century, K.G. Kristinsson et al. assumed that iodine complex with biologically active polymer matrix, for example, with chitosan, has better biocompatibility with human skin tissues in comparison with iodine adducts with synthetic polymers [44]. Some iodine-containing substances and materials based on organic polymers are presented in Table 2. However, native chitosan membrane has revealed several problems such as low porosity, poor mechanical strength and instability over long time, and low hydrophilicity [45].

Y. Tang et al. successfully obtained a stable iodide complex with chitosan (CTS) [46]. Iodization results revealed

TABLE 2

IODINE-CONTAINING SUBSTANCES AND MATERIALS BASED ON ORGANIC POLYMERS AND THEIR ANTIBACTERIAL AND FUNGICIDAL EFFECT

Names of substances and materials with iodine/iodides	The substance under study	Strains	Antibacterial and fungicidal effects	Reference
Gellan nanocomposite film with polysilicic acid enriched with iodine	Film thickness 0.75 ± 0.02 mm	*E. coli* MTCC 1652, *S. aureus* MTCC 7443	ZOI is 15 ± 1 and 17.3 ± 1 mm for *E. coli* and *S. aureus* strains, respectively.	[48]
Nanocomposite based on starch-reduced graphene oxide and polyiodide (SRGO-PI)	Thin SRGO-PI sheets in several layers with slight creasing	*E. coli* KCTC 2571, *S. aureus* KCTC 3881	The values of half-maximal inhibitory concentration (IC50) were 0.45 and 0.41 mg/mL for *E. coli* and *S. aureus*, respectively. MIC and MBC were 2.5 and 5 mg/mL, respectively, for both *E. coli* and *S. aureus*.	[51]
Porous polymers based on triazine with iodine (I_2@NRPOP-1 and I_2@NRPOP-2)	Porous polymers NRPOP-1 and NRPOP-2 consist of agglomerated spheres having different sizes and different pore densities	*E. coli* (155065A), *P. aeruginosa* (155250A), *M. luteus* (155155A)	ZOI values: in contact with NRPOP-1: for *E. coli* – 0.9 ± 0.1 mm; for *P. aeruginosa* – 1.8 ± 0.1 mm; for *M. luteus* – 2.7 ± 0.2 mm. In contact with NRPOP-2: for *E. coli* – 0.9 ± 0.1 mm; for *P. aeruginosa* – 1.8 ± 0.1 mm; for *M. luteus* – 2.0 ± 0.1 mm.	[54]
Iodine-containing arabinogalactan composite	Nanoparticles ranging in size from 26 to 200 nm	*E. coli* ATCC 25922, *K. pneumoniae* ATCC 700603, *P. aeruginosa* ATCC 27853, *S. aureus* ATCC 25923, *E. faecalis* ATCC 29212, *C. albicans* ATCC	MIC/MBC and MFC values: for *E. coli* - 0.62/1.25 mg/mL; for *P. aeruginosa* - 5/5 mg/mL; for *K. pneumoniae* - 5/5 mg/mL; for *S. aureus* - 1.25/5 mg/mL; for *E. faecalis* - 2.5/5 mg/mL; for *C. albicans* - 1.25/1.25 mg/mL.	[55]

Note. ZOI – inhibition zone; SRGO-PI – a nanocomposite based on starch-reduced graphene oxide with polyiodide; IC50 – semi-maximal inhibitory concentration; MIC – minimum inhibitory concentration; MBC – minimum bactericidal concentration; NRPOP – porous organic polymer based on triazine; MFC – minimum fungicidal concentration.

that the CTS – CTS – I_2 complex exhibited strong antibacterial activity against two bacteria, *E. coli* and *S. aureus*. The results revealed that the complex could have potential applications in biomedical fields such as drug delivery and wound dressing.

Chitosan treatment of polyacrylonitrile fibre material modified with hydroxylamine and iodine (PAN-GA-I_2) was recently undertaken to improve the physical and mechanical properties and water absorption capacity of these materials. It has consequently led to an increase in the strength and hydrophilicity of the material [47].

A nanocomposite film consisting of polysilicic acid, gellan and iodine was prepared and assessed in terms of antibacterial properties by R. Sharma et al. [48]. Gellan gum is an extracellular linear anionic heteropolysaccharide which is obtained via fermentation by the *Sphingomonas paucimobilis* microorganism. Such a carrier is of interest as it is biocompatible, biodegradable and mucoadhesive in nature. This complex showed antibacterial activity to a greater extent for *S. aureus* than for *E. coli*. It is expected to have future applications in pharmaceuticals. *In vivo* model studies are expected to further studies concerning their transformation into a suitable dosage form.

S.G. Sharipova et al. have studied the possibility of stabilization of iodine complex with chitosan by adding gellan gum to it. Since the stability constant increased by an order of magnitude, the authors considered that the presence of gellan gum in the system contributes to the stabilization of the complex [49].

Graphene oxide has long been proven as a carrier for antibacterial agents. It represents an extra-large organic molecule containing a two-dimensional carbon mesh. Graphene oxide particles are highly hydrophilic. They form stable aqueous dispersions over a wide range of concentrations, as well as stable dispersions in a number of organic solvents. Graphene oxide thin films have high optical transparency [50]. A new nanocomposite based on starch reduced graphene oxide with polyiodide showed equally good bactericidal effect against pathogenic gram-negative *E. coli* and gram-positive *S. aureus* bacteria [51]. Such nanomaterial can be used for food packaging.

The effect of multi-walled carbon nanotubes (MWCNTs) functionalized with iodine (15, 10 and 5 wt%) on *E. coli* species and MCF-7 breast adenocarcinoma tumor cells was also studied. By modifying with 15 and 10 wt% iodine, the MWCNTs became significantly antimicrobial active and the survival rate of *E. coli* at concentrations of 0.1 and 0.01 g/L was less than 2 %, while the rate for MWCNTs without iodine was 7 and 30 %, respectively. Reducing the amount of iodine to 5 % slightly reduced the biocidal effect. By comparing the effects of iodine within MWCNTs and pure iodine, the cytotoxic effect of pure iodine was much higher than that of MWCNTs containing iodine in the same concentrations [52].

A.A. Zubenko et al. proposed activated carbon as an iodine carrier eliminating its toxic effect and studied the effect of this complex against *E. coli* and *S. aureus* species. The results revealed that this preparation with 14.5 % iodine content had bacteriostatic activity comparable to that of other preparations (Iodinol and potassium iodide) [53].

The development of porous materials that adsorb iodine has recently become a popular trend as they can provide both its storage and subsequent release. Triazines comprise a class of heterocyclic compounds. Triazine-based porous organic polymers (I_2@NRPOP) with iodine may be promising as antibacterial agents for environmental remediation and drug delivery system [54]. These polymers have the ability to trap iodine vapour back and adsorb it. Iodine loaded polymers demonstrated good antibacterial activity against *Micrococcus luteus*, *E. coli* and *P. aeruginosa* to the same extent.

A method for the preparation of a nanocomposite containing iodine in a natural polymer, arabinogalactan, at a concentration of 13.97 % was recently described [55]. The nanocomposite was most effective against *E. coli* strain ATCC 25922, and least effective against *P. aeruginosa* ATCC 27853 and the ESBL-producing test microorganism *K. pneumoniae* ATCC 700603. Assessment of the inhibitory and fungicidal effects of the nanocomposite revealed its antifungal activity against *C. albicans*. Along with known halogen-containing compounds traditionally used in medicine, this water-soluble composite material of increased stability also has a prospect of use in medical practice and in the development of innovative domestic antimicrobial drugs.

Another study used aqueous dispersions of iodine (18 %) included in a matrix of arabinogalactan at six concentrations (0.1, 0.01, 0.001, 0.0001, 0.00001 and 0.000001 g of starting substance in 1 mL of suspension) [56]. The antimicrobial effect of nanoparticles was studied using five *E. coli* cultures with different biochemical properties (*E. coli* with normal enzymatic activity (NFA) – 3 autostrains; *E. coli* with weak enzymatic activity (WFA) – 1 strain; *E. coli* with hemolytic activity – 1 strain). In a sensitivity assay to iodo-arabinogalactan nanoparticles, *E. coli* showed antibacterial activity against all strains tested only at a concentration of 0.1 g of starting substance in 1 mL of suspension and against two *E. coli* strains NFA and WFA at a concentration of 0.01 g/mL. The authors suggest that the size of the nanoparticles, incompatibility of the arabinogalactan matrix with iodine, or resistance of the strains tested may have contributed to the low efficacy of the complex in this study.

Pectin has the ability to act as a polymeric carrier as a result of its bioactivity and safety. Intermolecular interactions of iodine with low-methoxylated apple pectin modified with pharmacophores were studied. Stable iodine-containing complexes have been obtained on the basis of pharmacophore-containing low-methoxylated pectins with antibacterial activity and prolonged iodine release [57].

V.I. Kostin et al. reduced iodine toxicity via complexation with amaranth pectins. As a result, complexes of iodine, potassium iodide-iodide with amaranth pectin were obtained in a 1:6 ratio (one iodine molecule per six monosaccharide

moieties). In the course of this study, iodine was found to form several types of stable complexes with amaranth pectins. It was found that the obtained complexes of pectin with iodine are superior to iodinol and other iodine preparations in their effectiveness in terms of bacteriostatic action [58].

A.N. Sabitov et al. synthesized a new antimicrobial compound in the system tryptophan – iodine – sodium iodide – water. Cytotoxicity test on MDCK cell culture and determination of mutagenic activity of the complex on L5178Y cell line confirmed the safety of this compound. The complex demonstrated bactericidal activity against both sensitive and multi-drug resistant bacterial strains in the range of 125–250 μg/mL. The test was performed on *S. aureus* ATCC 6538-P; *S. aureus* ATCC BAA-39; *E. coli* ATCC 8739; *E. coli* ATCC BAA-196; *P. aeruginosa* ATCC 9027; *P. aeruginosa* TA2. This complex has the potential to be used as an antimicrobial agent since its low cytotoxicity and antimicrobial activity [59].

Studies in the area of antimicrobial activity of organometallic compounds have expanded in recent years. Some iodine-containing substances and metal-based materials and their antibacterial effects are summarized in Table 3. A.N. Au-Duong et al. developed iodine-enriched zeolite imidazolate framework-8 (ZIF-8), which proved to be an effective bactericide [60]. The result was observed at pH = 6.0 for 3 min, however no appreciable antimicrobial activity could be revealed at pH > 7.0. Gram-negative *E. coli* strain, gram-positive *Staphylococcus epidermidis* and *S. aureus* were killed at a concentration of 0.2 g/L. This is assumed to be a promising protective compound for coating surfaces to prevent bacterial biofilm formation.

TABLE 3

IODINE-CONTAINING SUBSTANCES AND MATERIALS BASED ON METALS AND THEIR ANTIBACTERIAL EFFECT

Names of substances and materials with iodine/iodides	The substance under study	Strains	Antibacterial effect	Reference
Copper iodide nanoparticles	Nanoparticles with an average size of 8 nm	*B. subtilis* ATCC 6633, *S. aureus* ATCC 29737, *E. coli* ATCC 10536, *Shigella dysenteriae* ATCC 12039, *E. coli* DH5α (K12), *E. coli* (EC 505970)	MIC/MBC values: for *E. coli* DH5α – 0.066/0.083 mg/mL; for *E. coli* – 0.1/0.11 mg/mL; for *S. aureus* – 0.1/0.15 mg/mL; for *E. coli.* (EC 505970) – 0.1/0.11 mg/mL; for *S. dysenteriae* – 0.1/0.11 mg/mL; for *B. subtilis* – 0.15/0.18 mg/mL.	[64]
Zeolite imidazolate framework-8, enriched with iodine (ZIF-8@I)	ZIF-8@I nanoparticles are about 530 ± 105 nm in size. ZIF-8 has the shape of a rhombic dodecahedron	*E. coli, S. aureus, K. pneumoniae* and *P. aeruginosa*	The tested strains were killed at a concentration of 0.2 g/L and pH = 6 for 3 min.	[60]
Microgranules of MOF composites passively releasing iodine	Composite MOF UiO-66 microgranules containing encapsulated gold nanorods coated with silica shells doped with iodine	*E. coli, S. aureus*	The concentration of iodine in AuNR@SiO_2@UiO-66 was 0.9 mg(I_2) × mg^{-1}. ZOI for *S. aureus* growth is 31–33 mm; for *E. coli* growth – 24–26 mm.	[16]
Calcium titanate and alloys of calcium titanate with iodine	Nanolayer consisting of calcium titanate and rutile, about 1 μm thick with 0.7–10.5 % iodine on the surface	*S. aureus* MRSA, *S. aureus* ATCC 6538P, *S. epidermidis* ATCC 49134, *E. coli* IFO 3972	Complexes that had been enriched with 8.6 % iodine showed antibacterial activity (reduction rate > 99 %) against all strains; a 97.3 % reduction in MRSA was observed after soaking in PBS for 6 months.	[61]

Note. MIC/MBC – minimum inhibitory concentration/minimum bactericidal concentration; ZIF-8@I – iodine-enriched zeolite imidazolate framework-8; MOFUiO-66 – zirconium-based organometallic framework (UiO – Universitetet of Oslo); ZOI – zone of inhibition; MRSA – methicillin-resistant *Staphylococcus aureus*; PBS – phosphate-buffered saline solution.

MOF UiO-66 microgranules containing encapsulated gold nanorods coated with a silica shell (AuNR@SiO_2@UiO-66) developed by X. Han et al., adsorb and accumulate iodine in very high concentrations and can release it in two ways: slowly and passively in low concentrations or – when exposed to near-infrared light – quickly and actively in high concentrations [16]. The iodine concentration in the microgranules was 0.9 mg(I_2) × mg^{-1}. The diameters of the growth inhibition zones were larger against *S. aureus* than against *E. coli*. The inhibition areas under irradiation had a larger diameter than in the absence of irradiation. Compared to povidone iodine, the inhibition of bacterial growth by this composite film was higher at similar iodine concentrations. The results reveal the promising potential of this composite material for preventing nosocomial and other microbial infections, including coatings for medical instruments or hospital surfaces.

Iodine has the potential to be used as an antimicrobial component in prosthetic materials. It has been recently outlined that calcium titanate and calcium titanate alloys were successfully loaded with iodine and slowly released iodine over a period of 90 days [61]. The sample with an 8.6 % iodine content was tested according to ISO 22196 and revealed high antibacterial activity against *S. aureus* (MRSA), *S. aureus*, *E. coli* and *S. epidermidis*, which persisted for several months. Iodine-containing Ti and its alloys are both expected to be particularly useful for orthopaedic and dental implants, however, *in vivo* studies are still required.

Iodine-supported implants are proving to be very promising in the prevention and treatment of infections, even in the presence of large bone defects. These findings have been disclosed in a review article by K. Ong et al. [62]. It provides some examples about successful demonstration of the antibacterial action of iodine-supported Ti implants in a rabbit femur study. Fewer signs of *S. aureus* and *E. coli* infection and signs of inflammation were observed with iodine-supported Ti implants. The efficacy of iodine-supported Ti implants in the treatment of patients with spinal osteomyelitis, malignant bone tumour or pyrogenic arthritis is also being outlined in this study. No signs of infection were observed in all cases at the time of their most recent follow-up.

Iodine is also capable at forming antimicrobial compounds with metals such as silver, copper and zinc along with polymers [63–65]. These compounds have enhanced antimicrobial activity compared to iodine or metal alone. A complex compound based on silver and iodine, for example, has been developed. Test cultures of the following microorganisms were used in the experiment: *E. coli* ATCC 25922, *Salmonella enterica* subsp. *enterica* ATCC BAA-2162, *S. pneumoniae* ATCC 49619, *S. aureus* ATCC 6538. As a result, the antibacterial activity of the complex compound at 50% concentration against all test bacterial cultures was revealed [66].

A particular feature of copper iodide nanoparticles developed by A. Pramanik et al. comprises their ability to produce reactive oxygen intermediates [64]. Among the tested bacteria, *E. coli* DH5a was more sensitive and *B. subtilis* was more resistant to CuI nanoparticles. Membrane damage is the main mechanism for the bactericidal activity of these nanoparticles. They could potentially be applied in antibiotic therapy.

The complex of zinc iodide with Schiff bases synthesized by M. Montazerozohori et al. has antimicrobial activity against *E. coli* ATCC 25922, *P. aeruginosa* ATCC 9027, *S. aureus* ATCC 6538, *B. subtilis* ATCC 6633, *C. albicans* and *Aspergillus niger* [65].

The "green" synthesis has been recently increasing in popularity, with the key factor being the reduction of toxic impact on the environment. "Green" synthesis involves the use of bacteria, fungi, yeasts, algae or plants that are able to modify the properties of nanoparticles as a result of their metabolic processes. Biosynthesized silver iodide nanoparticles by M. Kannan et al. revealed complete biofilm deactivation at a concentration of 50 mg/mL [63]. Nanoparticles with a mean diameter of 21 nm inhibited the growth of gram-negative bacteria such as *E. coli*, *Vibrio cholerae*, *Salmonella typhi*, and *P. aeruginosa* at nanoparticle concentrations of 75 mg/mL or higher. Study of the mechanisms revealed that free radicals and oxidative stress were responsible for the antibacterial activity.

Silicone is actively used for medical purposes. To the extent that microbial cells adhere to the surface of silicone materials and form biofilms, methods for imparting antimicrobial activity to silicone materials have become in high demand. A method for antibacterial treatment of silicone membranes by a two-step process of immersion in iodine and silver nitrate solutions has recently been developed [67]. Silver iodide particles ranging in size from a few nanometres to a few tens of nanometres were present on the surface of the silicone membrane. Antibacterial activity against *E. coli* NBRC 3301, *S. aureus* NBRC 13276 remained high even after 10-fold acid treatment (pH = 2).

CONCLUSION

Since the heyday of antibiotic therapy with modern antimicrobials, iodine-containing antiseptics have become less popular in light of their increased toxicity. In response to the problem of high antibiotic resistance that has developed over time, however, the approach to the use of preparations in which iodine and iodides are the active ingredients has been reconsidered. Numerous data indicate that many diverse compounds of safe iodide preparations with no pre-existing deficiencies have been developed and have the potential to be used as highly active antimicrobial agents.

Being efficient and non-resistant, iodine is ideal for treating many infectious agents, including those that form biofilms. Iodine-containing compounds are of great interest because of possessing specific parameters, antibacterial and antifungal activity, and low cytotoxicity in various applications.

The literature data studied in this review represent the prospects of using iodine complexes that contribute to the prevention and treatment of infectious complications and diseases in a wide range of medical specialties,

reduce the risk of infection transmission, and prevent microbial growth (treatment and prevention of wound infections and postoperative complications in surgery, traumatology, dentistry, dermatology, burns in combustiology; prevention of superinfection in nosocomial infections, disinfection of operating rooms and injection fields of patients in preparation for surgical interventions and invasive examinations (biopsies, punctures, injections); hygienic treatment of the hands of surgeons and medical personnel, etc.), increasing the strength and durability of materials.

Also promising potential is the use of iodine complexes in the development of new antimicrobial drugs and materials, which in the future may be applied to control microbial activity and prevent the development of infections.

Conflict of interest

The authors of this article declare no conflicts of interest.

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