UDC – 615.33:615.32

ANTIMICROBIAL POTENTIAL OF "KAVALGINE" CLAY BASED NOVEL PREPARATION FOR PROPHYLACTIC SKIN CARE

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https://doi.org/10.56243/18294898-2024.1-3

Abstract

The demand for novel antimicrobial preparations is high in medicine, veterinary, agriculture, etc. However, numerous classical preparations derived from steroids, oligo-/macro- cyclic lactones, and antibiotics possess notable disadvantages: adverse effects on human health, the potential for ecological risks, etc. Moreover, the increase of antibiotic concentrations in environment escalates the multi-drug resistance problem. Therefore, the need of innovations in that scope, and particularly, the search for alternative new natural preparations is very actual.

The current paper discusses "Kavalgine" new preparation, developed using natural components: highly mineralized clay obtained during the table salt mining; propolis, laurel essential oil and other bioactive additives. Its effect was successfully tested on model strains of various opportunistic pathogens: *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, *Salmonella enteritidis*, and *Staphylococcus aureus*.

Keywords: highly mineralized clay sediments, propolis, antimicrobial effect, laurel essential oil, opportunistic pathogenic bacteria, skin health prophylactics.

Introduction

The development of a new, improved antimicrobial and anti-inflammatory preparation is a highly relevant topic in light of the current situation. This urgency arises due to the multiple drawbacks associated with conventional antibiotics used in medicine and other fields. Classical antibiotics often lead to various harmful side effects, reduced efficacy, allergies, and other undesirable consequences [1,2]. In this regard, the elaboration of novel safe skin care preparations and ointments, which are based on natural materials is especially important. That is one of the prospective strategies for the development of treatment preparations by the combination of inorganic mineral components from the natural sources (clays and non-clay minerals, etc.) with some organic plant and animal sourced substances of target effects, such as like propolis, plant essential oils, waxes and also fungi bioactive components, etc. [3,4].

For centuries, natural clay has been utilized as a traditional remedy for its anti-inflammatory properties. Its beneficial effects on the skin have been recognized and documented throughout history. Ancient civilizations like the Egyptians employed clay for treating wounds and addressing digestive issues [5]. The application of clay in medicinal practices extends to various traditional systems such as Ayurveda, Traditional Persian and Chinese medicine, etc. [6,7]. During the last decades, the use of clay in diverse fields of

medicine, cosmetology, and healthcare has witnessed a steady increase. Different types of clay with varying chemical compositions can be found depending on their geographical origins. These mineral-rich substances have long been employed for the treatment of skin infections, as evidenced by numerous studies conducted in recent decades [8]. Clay has the ability to bind to certain metals, including toxic heavy metals, thereby preventing their absorption by the body's organs such as the skin, stomach, and intestines [9]. French green clay, rich in Fe-smectite, is renowned for its healing properties against conditions like Buruli ulcer, a necrotizing fasciitis caused by *Mycobacterium ulcerans* [10]. Hence, clay is recognized for its anti-inflammatory capabilities. Additionally, apart from its anti-inflammatory effects, clay is known to improve digestion, enhance the immune system, and promote skin health [11, 12].

Propolis is also known for its wide application in various branches of traditional medicine in many countries. It is a resin-like substance produced by bees that has antimicrobial properties and other valuable bioactivities. Bees initially use propolis to protect their hives from pathogens. In human civilization propolis are being used for medicinal purposes for centuries. It has some antibacterial, antifungal, and antiviral properties, making it an effective natural remedy for fighting against infections [13, 14]. Propolis can be used to treat a wide range of pathological conditions, including sore throat, colds, flu, and even cancer [15]. It is also a natural source of antioxidants, which can help to protect the body from oxidative stress and inflammation. The mechanisms of its effect are defined by the interactions of phenolic and other compounds, including pinobanksin, pinocembrin, and galangin with cells. Moreover, the antibacterial activity is attributed to its active compounds, such as like the aromatic compounds, especially caffeic acid, lactones. and flavonoids. In addition, propolis has a bactericidal activity which able to inhibit the cellular division such as like to damage the cell walls of bacteria, and to suppress the protein synthesis. Pinocembrin is the component of propolis that demonstrates the antibacterial activity against some strains of Streptococcus spp. and other pathogenic bacteria [16-20]. Artepillin C, p-coumaric acid, 3-phenyl-4-hydroxycinnamoyl cinnamic acid are bale to decrease the activity of bacterial glycosyltransferase in some pathogenic bacteria, such as like Helicobacter pylori. Another one important component of propolis is apigenin. Apigenin is one of the most common flavones aglycones, a natural antioxidant with anti-inflammatory and anti-carcinogenic properties [21, 22]. Propolis also serves as a component of painkillers and preparations for the symptomatic treatment and the supporting therapy medicines of various diseases such as like: neuritis, neuralgia, osteochondrosis, radiculitis, arthropathy and other inflammatory diseases of the musculoskeletal system [23, 24]. Based on the considered literature data about the positive influence of clay and propolis on health in general, “Kavalgine” composition was elaborated in our laboratory, as a combination of highly mineralized clay, propolis and essential oil of laurel. In current paper the antimicrobial effect of “Kavalgine” ointment is studied.

Conflict Setting

Due to the decrease of efficiency of classical antibiotic therapy for the treatment of various infections the actuality of usage of alternative antimicrobials, such as like plant oils

and various natural extracts as well as inorganic salts and mineral compounds is being increased. That is why the studies of natural mineral clay sediments-based preparations are started to be more actual world around. And this is very important especially in scopes of cosmetology, dermatology and preventive prophylactic therapy. In these regards, the main purpose this research was to study the antimicrobial properties of new "Kavalgine" preparation against the range opportunistic pathogens of human, including the test-cultures of most dangerous opportunistic pathogens, such as like *Pseudomonas aeruginosa* and *Staphylococcus aureus*, which are well-known by the multi-drug resistance.

Materials and Methods

The name of preparation is coming from Armenian word “kav”, what means “the clay”. "Kavalgine" is elaborated as the combined effect ointment, consist of inorganic and organic active components of absolutely natural source. Inorganic ingredient of it is the major part and it is based on highly mineralized clay, which was obtained from the side product sediments of table salt production process (from Avan rock salt mine of RA). The initially isolated highly mineralized clay-sediments contain about 30 various micro- and macro-elements [25]. The detailed description of Cavalgine includes the following: alcohol solution of propolis, bay leaf esencial oil, clay Dimexidum in the following ration wt.%: 20% alcohol solution - 7.5-9.5; bay leaf esential oil - 0.5-2.0; Dimexidum - 7.5-9.5 and clay - the rest [26].

The organic components of “Kavalgine” are essential oil of laurel and the natural bee product propolis. Also, it contains Dimexide (dimethyl sulfoxide or DMSO) which was used as an additive to improve skin tissue permeability [27]. All these compounds are added to enhance anti-inflammatory, pain-relieving and antimicrobial target effects of the ointment.

For qualitative evaluation of antibiotic-resistance of the selected microbial strains, there were used the sterilized by autoclaving solid selective media, based on beef-extract agar with addition of 50 mcg/mL content of appropriate antibiotic. The following antibiotics were used in selective m In this research for in vitro microbiological experiments, 10 strains of human Gram-negative and Gram-positive opportunistic pathogens from the National Collection of Microorganisms of Microbial Depository Center (MDC), “Armbiotechnology” Scientific and Production Center (SPC) of the National Academy of Sciences of the Republic of Armenia (NAS RA) were used. The following bacterial strains were selected as objects for tests: *E. coli DH5α S. enteritidis 5170 K. pneumonia 5244 St. aureus 5233 P. aeruginosa 5249 P. aeruginosa 9056 S. maltophilia 9289 P. fluorescens 9134 P. putida 9235 P. geniculate 9340.* All the mentioned bacterial strains were cultivated on liquid Luria-Bertani medium (LB) and solid nutrient L-agar cultural media (1.8%-agar) due to the generally accepted methodologies, using 60 mm diameter Petri dishes [28].

edia: Pcn/Penicillin; Amp/ampicillin, Amx/amoxicillin, Amc/augmentin (representatives of aminopenicillins of β-lactam antibiotics), Cfx/cefixime, Cro/ceftriaxone (representatives of I and III generations cephalosporins of β-lactam antibiotics), Kan/kanamycin, Stp/streptomycin, Cip/ciprofloxacin (representatives of aminoglycoside antibiotics), Cam/chloramphenicol (of amphenicol antibiotics) and Azm/azithromycin (from azalides of macrolides antibiotics), produced by “Asteria”. The cultivation on appropriate

selective media was carried out by streaking technique, using 60 mm diameter Petri dishes, at 37 °C (in contribution to the optimum conditions of the studied bacterial strain), under aerobic conditions [29]. For the assessment of antimicrobial activity of "Kavalgine" ointment, two methods were used. The preliminary screening of "Kavalgine" effect was carried out by the method of mixing ointment with the cultural media inappropriate concentrations. After the solidifying of the obtained mixture, the microorganisms were cultivated on it by the stacking method. Also, for the antimicrobial effect assessment the method of wells and was applied. For that purpose, 1.8%-agar containing MPA (meat peptone agar) cultural media was poured into Petri dishes (60 mm diameter). Then the sterile glass cylinders were placed in a center of each of Petri dishes. Separately the mixtures of appropriate microbial strain overnight cultures (~108 CFU) and the molten 0.7% agar containing MPA at 37 °C, were prepared in sterile test tubes. On surface of solidified 1.8%-MPA cultivation media in each of Petri dishes, the mentioned mixture was added as the second layer, around the placed glass cylinders. After the solidifying of second layer, the glass cylinders were carefully taken off for the obtaining od wells. In each of obtained well 1.2 mg of testing ointment was added.

For each strain the experiment was carried out in two ways: with UV-sterilized (4 min upon the λ = 254 nm UV light) ointment samples and without the UV-sterilization. As a control in all the experiments, which were carried out, the sterile water and DMSO appropriate quantities were added instead the testing "Kavalgine" ointment [30, 31]. for a comparable quantification of a qualitative analyses of "Kavalgine" ointment effect on the studied microorganisms the digital analysis of results was performed by ImageJ software [32]. The statistical assessment was based on the fact that all the experiments were carries out in 5 series of 3 repeats for each probe. MS Excel was used for data analysis of "Kavalgine" antimicrobial effect evaluation. The data of growth inhibition zones are given in mm (table 1, fig. 1-2), SEM (Standard Error of the Mean) were ± 0.23-0.37. Significance was tested by applying Student t-test and estimated as p-value less than 0.05.

Research Results

The results of antimicrobial resistance tests of bacteria which were used for this research are presented in tab. 1 and fig. 1.

During all the experiments, it was noted non-significant inhibition of growth of all the tested bacterial cultures. Only in case of *K. pneumonia 5244*, after 24 hours, a thin sterile rim 6 mm wide was formed around the well, which indicates a slight antibacterial effect. After 3-4 days of experiment in *K. pneumoniae 5244* sample, the width of the sterile rim was reached 5 mm. In *P. aeruginosa 5249* and *P. aeruginosa 9056* samples, the rims were 1.5 mm and 1.2 respectively. For the rest of the samples: *E. coli DH5α, S. enteritidis, St. aureus 5233, S. maltophilia 9289, P. fluorescens 9134, P. putida 9235, P. geniculate 9340* the mean of the measured width was 1 mm.

The obtained results indicate the lower intensity of "Kavalgine" ointment antimicrobial effect on the mentioned bacteria growth. Throughout the experiment, in all the cases of unsterilized ointment, the contamination with very small colonies of an undefined contaminant microbes was observed. That indicates the absence of a significant antimicrobial

effect not only in relation to the tested cultures, but also to the contaminant. In case of sterilized ointment samples, contamination was not observed. All the control samples have demonstrated the absence of notable antimicrobial effect of DMSO on the research strains of bacteria.

Table 1

Antibiotic-resistance of human opportunistic pathogenic bacterial strains.
S – sensitivity, R – resistance; C – control, "+" – growth of strain in full surface of petri dish (d = 60 mm) on nutrient agar cultural media with addition of appropriate quantity of sterile water; antibiotics: Pcn - penicillin, Amx - amoxicillin, Amp- ampicillin, Amc - augmantine, Cfx - cefixime, Cro - ceftriaxone, Cam - chloramphenicol, Cip - ciprofloxacin, Stp - strepromycin, Kan- kanamycin

Bacterial strain	Antibiotics										C
	Pcn	Amx	Amp	Amc	Cfx	Cro	Cam	Cip	Stp	Kan	
E. coli DH5α	S	S	S	S	S	S	S	S	S	S	+
S. enteridіdis 5170	S	S	S	S	S	S	S	S	S	S	+
P. aeruginosa 5249	R	R	R	R	R	R	R	S	R	R	+
K. pneumonia 5244	R	R	R	R	R	S	R	S	S	S	+
St. aureus 5233	R	R	R	R	R	S	R	S	R	R	+
Rh. javanica 1002	R	R	R	R	R	R	R	R	R	R	+
B. thuringiensis 849	R	R	R	R	R	R	R	S	R	S	+
Br. laterosporus 200-4	S	S	S	S	R	S	S	S	S	S	+

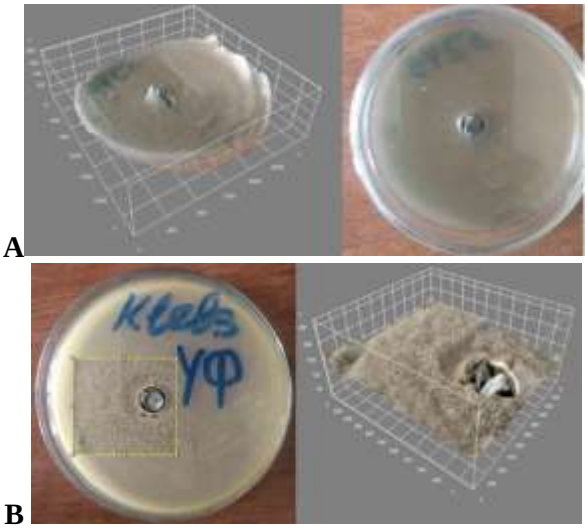

Fig. 1 Photography of "Kavalgine" antimicrobial activity observation *in vitro* and digitizing of it
A – *P. aeruginosa 5249*; B – *K. pneumonia 5244*.

According to the presented data, the majority of them are multi-drug resistant or pan-drug resistant. The results of antimicrobial activity of «Kavalgine» preparation against the ten common opportunistic pathogens of human are presented in tab. 2 and fig. 2.

During the experiments with UV sterilization and with the sterilization by UV light, it was found out that there is no differences between the collected data. Thus, the sterilization has no impact on an influence of preparation. It can be assumed that in the absence of a

pronounced antibacterial effect, the healing effect of the ointment may be caused by the effect of organic components (wax, etc.) of propolis on the skin. It is also possible to assume a regeneration-stimulating effect of clay and other mineral components on the skin. Probably, the considered ointment beneficial effect is caused by all the natural additives combined presence influence, due to their improving of antimicrobial properties of the clay basic component. Thus, the beneficial effect of «Kavalgine» ointment on the skin is probably prognosed [33].

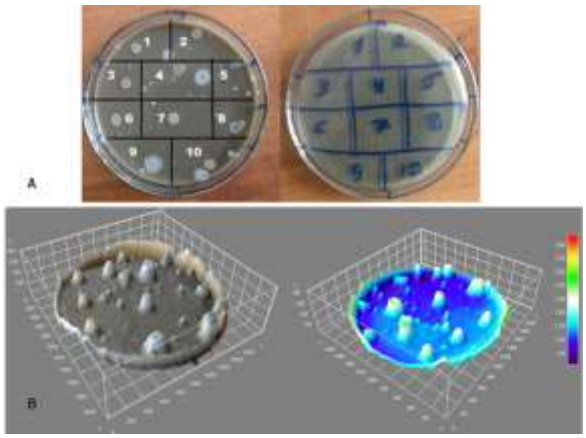

Fig. 2 «Kavalgine» antimicrobial effect on opportunistic pathogens

A. "Kavalgine" (without UV sterilization) effect on microbes: 1 – *E. coli DH5α*, 2 – *S. enteritidis 5170*, 3 – *K. pneumonia 5244*, 4 – *St. aureus 5233*, 5 – *P. aeruginosa 5249*, 6 – *P. aeruginosa 9056*, 7 – *S. maltophilia 9289*, 8 – *P. fluorescens 9134*, 9 – *P. putida 9235*, 10 – *P. geniculate 9340*; B – Results digitizing by thermal imaging.

Table 2

Antimicrobial activity of "Kavalgine" against the opportunistic pathogens

"+" – the presence of growth and the absence of antimicrobial effect on all the diameter of Petri dish (d = 60 mm); "C+" – Positive control on nutrient agar cultural media without any antimicrobial compound; C_{water} – control with sterile water; C_{DMSO} – control with sterile DMSO.

Bacterial Strain	Effect of "Kavalgine" without UV sterilization	C+	C_{water}	C_{DMSO}
E. coli DH5α	1 mm	+	+	+
S. enteritidis 5170	1 mm	+	+	+
K. pneumonia 5244	5 mm	+	+	+
St. aureus 5233,	1 mm	+	+	+
P. aeruginosa 5249	1.5 mm	+	+	+
S. maltophilia 9289	1 mm	+	+	+
P. fluorescens 9134	1 mm	+	+	+
P. putida 9235	1 mm	+	+	+
P. geniculate 9340	1 mm	+	+	+
P. geniculate 9056	1.2 mm	+	+	+

For the comparison of propolis and its mixture in consistence of "Kavalgine" preparation, the activity of it was separately tested upon the same conditions by the same methods which were mentioned above on same ten bacterial strains. In case of application of well method, to propolis on the first day, a sterile rim with 1 mm wide was formed around the well on samples of *K. pneumonia 5244.* After 48 hours of experiment, in the samples of *St.*

aureus 5233 1 mm wide rim was formed. In sample of *K. pneumonia 5244* the rim was enlarged up to 1.5 mm. In case of usage of method of adding the propolis in cultural media, only in case of UV-sterilized samples the growth suppression of *K. pneumonia 5244* (after 24 hours of experiment) and *S. maltophilia 9289* (after 48 hours of experiment) were noted. According to the literature data propolis containing preparations have a positive effect on wound and sport trauma healing [34, 35].

Therefore, based on the obtained results, «Kavalgine» new preparation might be also recommended as a preparation for increasing of wound healing processes intensity, especially for usage in sport medicine.

Conclusion

The elaborated «Kavalgine» preparation, which is originally based on mineral-reach clay sediments and the bee product propolis have demonstrated not so emphasized antimicrobial activity. The maximal effect was noted for strains *K. pneumonia 5244, S. maltophilia 9289, P. aeruginosa 9056, P. aeruginosa 5249, St. aureus 5233.* The experiments with propolis have demonstrated the similar results. In general, the use of clay and propolis as a natural anti-inflammatory treatment for overcoming antimicrobial resistance against pathogens offers a safe and effective alternative to conventional medicine.

These natural remedies have been used for centuries and have been shown to have a wide range of therapeutic properties. By incorporating clay and propolis into your daily routine, you can help to reduce inflammation, boost your immune system, and promote overall health and wellness. Probably, the main target of “Kavalgine” effect is cellular growth of host-organism and the signification of general immune status of it.

Probably, the considered ointment beneficial effect is caused by all the natural additives combined presence influence, due to their improving of antimicrobial properties of the clay basic component. Thus, «Kavalgine» new anti-inflammatory preparation is recommended for further in vivo experiments and the clinical research for deeper understanding the mechanisms of its effect, which were demonstrated during the *in vivo* experiments.

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ՄԱՇԿԻ ԿԱՆԽԱՐԳԵԼԻՉ ԽՆԱՄՔԻ ՀԱՄԱՐ «ԿԱՎԱԼԳԻՆ» ԿԱՎԱՅԻՆ ՀԵՆՔՈՎ ՆՈՐ ՊԱՏՐԱՍՏՈՒԿԻ ՀԱԿԱՄԱՆՐԷԱՅԻՆ ՆԵՐՈՒԺԸ

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Նոր հակամանրէային պատրաստուկների պահանջարկը մեծ է բժշկության, անասնաբուժության, գյուղատնտեսության և այլ ոլորտներում: Այնուամենայնիվ, ստերոիդներից, օլիգո-/մակրո-ցիկլիկ լակտոններից և հակաբիոտիկներից ստացված բազմաթիվ դասական պատրաստուկներ ունեն զգալի թերություններ. բացասական ազդեցություն մարդու առողջության վրա, էկոլոգիական ռիսկեր և այլն: Ավելին, հակաբիոտիկների կոնցենտրացիաների աճը շրջակա միջավայրում սրում է բազմակայունության հիմնախնդիրը: Ուստի այս ոլորտում նորարարությունների անհրաժեշտությունը և մասնավորապես այլընտրանքային նոր բնական պատրաստուկների որոնումը շատ արդիական է:

Հոդվածում քննարկվում է բնական բաղադրիչներ՝ կերակրի աղի արտադրության ընթացքում անջատված բարձր հանքայնացված կավի, պրոպոլիսի, դափնու եթերայուղի և այլ կենսաակտիվ հավելումների կիրառմամբ մշակված «Կավալգին» նոր

պատրաստուկը: Դրա ազդեցությունը հաջողությամբ փորձարկվել է տարբեր պայմանական պաթոգենների մոդելային շտամների վրա: *K. pneumonia, P.aeruginosa, S. enteritidis* և *S. aureus*:

Բանալի բառեր. բարձր հանքայնացված կավե նստվածք, պրոպոլիս, հակամանրէային ազդեցություն, դափնու եթերայուղ, պայմանական պաթոգեն բակտերիաներ, մաշկի առողջության պրոֆիլակտիկա:

АНТИМИКРОБНЫЙ ПОТЕНЦИАЛ НОВОГО ПРЕПАРАТА НА ОСНОВЕ ГЛИНЫ «КАВАЛГИН» ДЛЯ ПРОФИЛАКТИЧЕСКОГО УХОДА ЗА КОЖЕЙ

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Спрос на новые антимикробные препараты высок в медицине, ветеринарии, сельском хозяйстве и др. Однако многие классические препараты на основе стероидов, олиго-/макроциклических лактонов и антибиотиков имеют ряд недостатков: негативные для здоровья последствия, потенциальные экологические риски и т.д. Более того, увеличение концентрации антибиотиков в окружающей среде усугубляет проблему мультирезистентности. Поэтому потребность в инновациях в этой области и в частности, поиск альтернативных новых натуральных препаратов весьма актуальны.

В данной статье рассматривается новый препарат «Кавалгин», разработанный с использованием натуральных компонентов: высокоминерализованной глины, полученной при добыче поваренной соли, прополиса, эфирного масла лавра и др. биоактивных добавок. Его действие было успешно протестировано на модельных штаммах разных условных патогенов: *K. pneumonia, P. aeruginosa, S. enteritidis* и *S. aureus.*

Ключевые слова: высоко-минерализированные осадки глины, прополис, антимикробный эффект, масло лавра, условно-патогенные бактерии, профилактика здоровья кожи

Submitted on 06.10.2023
Sent for review on 10.10.2023
Guaranteed for printing on 25.03.2024