კვლევის მიზანს წარმოადგენდა თბილისის საქალაქო ტრანსპორტზე და მის მომსახურებაზე დასაქმებულთა სამუშაო გარემოს ჰაერის მტვრითა და ტოქსიკური აირებით დაბინძურების მდგომარეობის ჰიგიენური შეფასება.

თბილისის მუნიციპალური ტრანსპორტის სამუშაო გარემოში შესწავლილია მტვრის და ქიმიური ნივთიერებების შემცველობა სამუშაო ზონის ჰაერში. ჰაერის ნიმუშების ანალიზისთვის გამოყენებულია ჰიგიენურ პრაქტიკაში აპრობირებული შესაბამისი მეთოდები. მტვრის და ტოქსიკური ნივთიერებების შემცველობა ჰაერში გამოკვლეულია როგორც ავტოტრანსპორტზე დასაქმებულთა (მძღოლები), ასევე, საშემკეთებლო საამქროებში სხვადასხვა პროფესიით მომუშავეთა სამუშაო ადგილებზე.

ჩატარებული კვლევის შედეგად მტვერის ყველაზე მაღალი დონე დაფიქსირდა მძღოლის სამუშაო ზონის ჰაერში; მოცემულ სამუშაო ადგილზე შრომის პირობები შეფასდა,როგორც მავნეობის 3.1 კლასი. პირობები საშემკეთებლო საამქროს სხვადასხვა უბანზე, ჰაერში მტვერის კონცენტრაციის დონის მიხედვით, შეფასდა შრომის პირობების მავნეობის 3.1 კლასით. შესწავლილი მაჩვენებლების მიხედვით, საშუალო სიდიდეებით, შრომის პირობების მავნეობის 3.3 და, მით უფრო - 3.4 კლასი არ გამოვლენილა.

კვლევის შედეგები საფუძვლად შესაძლოა დაედოს სამუშაო გარემოს მდგომარეობის გაჯანსაღებისკენ მიმართული პრევენციული ღონისძიებების შემუშავებას.

CHEMICAL MODIFICATION OF BROMELAIN WITH DEXTRAN ALDEHYDE AND ITS POTENTIAL MEDICAL APPLICATION

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Bromelain is a proteolytic enzyme found in almost all parts of the Pineapple plant (*Ananas comosus* L. Merr.) including the stems, fruits and leaves, from which the stem and fruit contain the highest concentrations of enzyme. It is a mixture of different thiol endopeptidases and other components like phosphatases, glucosidase, peroxidases, cellulases, glycoproteins, carbohydrates, and several protease inhibitors. Bromelain has been categorized as stem bromelain (EC. 3.4.22.32) and fruit bromelain (EC.3.4.22.33) based on its source. The molecular weight of stem and fruit bromelain is 23.8 kDa and 33 kDa respectively [16].

Clinical studies have shown that bromelain may help in the treatment of several disorders. An *in* silico and in vitro study of the bromelain-phytochemical complex inhibition of phospholipase A2 has shown that bromelain possesses anti-inflammatory properties [20]. A combination of bromelain, trypsin, and rutin was compared to diclofenac in patients with osteoarthritis of the knee by Akhtar N. et al (2004). After six weeks, both treatments resulted in significant and similar reduction in the pain and inflammation [4]. Clinical trials have shown that oral bromelain (500 mg/day) can be effective in the reduction of pain at the donor site after FGG and may also enhance wound healing [19].

The antioxidant activity of crude bromelain was shown by Saptarini N. et al. [18]. Bromelain prevents or minimizes the severity of angina pectoris and transient ischemic attack (TIA). It is useful in the prevention and treatment of thrombophlebitis [13].

Pillai K. et al. [15] have studied anticancer properties of bromelain with therapeutic potential against malignant peritoneal mesothelioma. This work has revealed that the activity of chemotherapeutic drugs in combination with romelain is enhanced. Romano et al. [17] investigated the possible antiproliferative/proapoptotic effects of bromelain in a human colorectal carcinoma cell line and its potential chemo-preventive effect on colon cancer. In addition, bromelain improves the absorption of antibiotics [16].

Proteolytic enzyme can be used to avoid this problem. Chemical modification of the protein molecules increases their stability [5] while decreasing antigenic, immunogenic and allergic effects. After chemical modifications of peanut proteins their allergenic potency was decreased as shown by [6].

Few studies have been published on modification of bromelain and previous work has only focused on changing the physical and chemical properties. Initial work in this field was published in 1975. Ota S. et al., carried out chemical modification of stem and fruit bromelain with 2-hydroxy-5-nitrobenzyl bromide, tetranitromethane, and hydrogen peroxide [14]. In another research the authors tried to obtain linear cross-linking of bromelain molecules. Modification was carried out with a bifunctional compound - glutaraldehyde (GTA), which reacts with the free amine groups of lysine. The degrees of covalent modification were 43% and 61%. Proteolytic activity was not changed and modified bromelain was more stable under heating [7]. Gupta P. and Saleemuddin M. [8] successfully performed oriented immobilization of stem bromelain via lone histidine on metal affinity support. In another study chemical modification of bromelain was carried out by using two reagents - Pyromellitic anhydride acid and Poly (maleic anhydride). The modification enhanced the stability and the optimum pH value shifted towards the alkaline. The thermal stability and the resistance to alkali and surfactants were increased by acylating the free amine groups of lysine [21].

Many water-soluble polymers are used for the chemical modification of enzymes. One such polymer is dextran. Dextran is a polysaccharide formed by poly-α-D-glucosides of microbial origin having glycosidic bonds predominantly C-1→C-6, as defined by the IUPAC. The large size of dextran molecules produces a significant change in the physical and chemical properties of the enzyme's surface with a minimal change to its chemical properties, therefore allowing an alteration in many of the functional properties of the enzymes. The use of the periodate-anion for oxidative cleavage of dextrans was first reported by L. Malaprade as early as 1928 [12].

The standard methodology for coupling proteins and other biomolecules to dextran aldehyde is by a reaction of pendant aldehyde groups of dextran aldehyde with nucleophilic residues, mainly amine groups of lysine residues, to create a reversible [9,11]. For example, streptokinase conjugated to dextran – streptodekase, was created and immobilized on a water-soluble matrix, which is much more stable in the physiological environment and causes less toxic and allergic reactions. The antigenic effect of streptodekase is reduced about 30 times [3]. Chemical modification of Papain was realised by conjugation with water-soluble, biocompatible and biodegradable polymers - oxidized dextran and with biodegradable polymers based on L-lysine. It has been shown that papain modified by those polymers had higher stability and proteolytic activity than native papain [2]. In another research effort, glucoamylase from *Aspergillus niger* was modified with dextran aldehyde, with the goal of getting a high cross-linking degree that permitted the enhancement of enzyme stability [10].

The aim of this study was to obtain a more stable and less allergic form of bromelain from commercially available product, via the modification of its chemical structure with a polysaccharide in order to change it's physical, chemical and biological properties. Dextran aldehyde was chosen as modification agent.

Material and methods. Commercial bromelain obtained from the stem of the Pineapple plant (*Ananas comosus* L. Merr.) was purchased from Beijing Wisapple Biotech Co., Ltd; dextran (molar mass 35 -40 kDa), sodium borohydride, potassium periodate, L-cysteine and Sephadex G-75 – from Sigma Aldrich, Casein – from Carl Roth.

Spectrophotometric determination was conducted in quartz cuvettes (10 mm), on a Jasco V-730 UV-Vis spectrophotometer. The spectra were automatically processed by UV-Probe system software (version 2.14.02). pH was determined by a Milwaukee - Mi 150 pH meter. Fraction collector LKB 2070 Ultrorac II. Freeze dryer VaCo 2.

Obtaining the protein enriched fraction of bromelain. In order to obtain purified bromelain (enriched with protein) from commercial bromelain protein precipitation method by alcohol was used, namely: 96% ethanol was cooled to -10^{0}C and added drop wise to the crude extract of commercial bromelain until the desired concentration (30 to 70% v/v) was reached. Then a small amount of distilled water was added to moisten the sample followed by lyophilization.

Gel filtration of bromelain (purified by precipitation with ethanol) on a Sephadex G-75. Gel filtration of the bromelain's aqueous solution was carried out on a Sephadex G-75 column (1.3x20cm) with phosphate buffer pH 8,0 (1/15 M).

Determination of protein concentration in bromelain. Protein concentration in bromelain was determined by the Extinction coefficient method [8].

Obtaining dextran aldehyde. Dextran was oxidized to dextran aldehyde by using potassium periodate. 1g of dextran was dissolved in 15ml of distilled water and to that 0.35g potassium periodate was added. The solution was incubated for two hours at room temperature under constant stirring, followed by dialysis and lyophilisation.

The chemical modification of bromelain with dextran aldehyde. The aldehyde group interacts with the free amino group of lysine of the protein molecule forming an imine group. The reduction of this latter group is performed by sodium bromide hydrate. For the chemical modification of bromelain, 40mg of dextran aldehyde were dissolved in 2 ml of phosphate buffer pH 8.0 (1/15 M) and 16 mg of purified bromelain dissolved in 2 ml of the same buffer were added. Incubation was performed at +4˚C for 20 hours under constant stirring. 5-7 mg of Sodium Borohydride was added for restoring double bonds, followed by 1 hour of incubation under constant stirring. Afterwards gel filtration of the sample was carried out on Sephadex G-75.

The chemical modification of bromelain with dextran aldehyde with cysteine. 5-6 mg of cysteine were added to 2 ml of bromelain's solution and modification performed as described above.

Determination of proteolytic activity of native and modified bromelain. The proteolytic activity of native and modified bromelain was determined by the universal protease activity assay: For bromelain enzymatic activity measurement, casein was used as substrate at 40 ◦C for 10 min. The reaction was then interrupted by the addition of trichloroacetic acid. The obtained mixture was filtred and measured at 280 nm. Enzymatic activity was calculated in activity units (U/mL) [1].

The pH optimum of the proteolytic activity of native and modified bromelain was determined by the above mentioned method on the different pH (6.5; 7.0; 7.5; 8.0; 8.5; 9.0). The temperature optimum of the proteolytic activity of native and modified bromelain was determined by the above mentioned method at different temperatures (40^{0}C; 50^{0}C; 60^{0}C; 70^{0}C; 80^{0}C). All samples were measured in triplicate.

Results and discussion. The protein fraction used in the modification reaction was obtained from commercial bromelain by precipitation by alcohol with a yield of 55-60%.

In commercial bromelain the concentration of the protein determined by the Extinction coefficient method was 54-55%, whereas in the purified Bromelain the concentration reached 74-75%. Gel-filtration of bromelain and modified bromelain on sephadex G-75 was performed in order to determinate the degree of bonding. As shown in Fig.1, after gel filtration of bromelain only one fraction-peak was obtained, whereas after gel filtration of modified bromelain with dextran aldehyde revealed two fraction-peaks. The optimal weight ratio of dextran aldehyde: bromelain was – 2.5 : 1. Chemical modification was carried out at pH 7.0 and pH 8.0. No significant differences were found while changing pH.

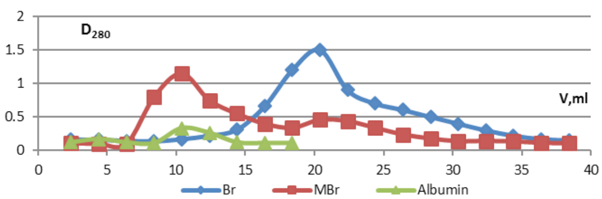

Fig .1. Gel-filtration of modified bromelain by dextran aldehyde on sephadex G-75. t - native bromelain (23.8 kDa), n - modified bromelain (MBr) (60-65 kDa), - Albumin (67 kDa). y -axis: optical density; x -axis: volume of fraction; values represent the average of triplicate measurements

From Fig 1. it is clear that the chemical modification of bromelain with dextran aldehyde took place. and the degree of bonding was 65±5%.

The proteolytic activity of modified bromelain was only 50±5% of native bromelain. In order to increase the proteolitic activity, cysteine was added to the enzyme solution. The addition of cysteine raised the activity of modified bromelain up to 70±5%.

The physical and chemical properties of modified bromelain (enzymatic activity, pH, the temperature optimum and stability) were studied. The study of the dependence of proteolytic activity on reaction conditions has shown that the pH optimum for native bromelain was 7.5, whereas for modified bromelain it was shifted towards 8.5 (Fig.2) and the temperature optimum for both modified and native bromelain was 60˚C. (Fig. 3).

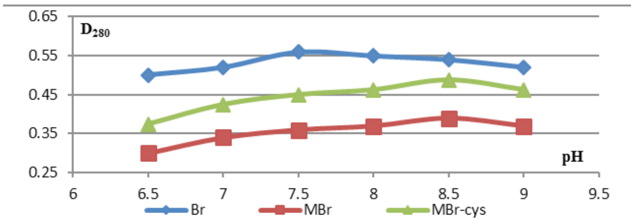

Fig 2. Dependence of proteolytic activity on pH. t - native bromelain (Br), n - modified bromelain (MBr), - modified bromelain with cysteine (MBr-Cys). y -axis: optical density; x -axis: pH during proteolytic activity measurement; values represent the average of triplicate measurements.

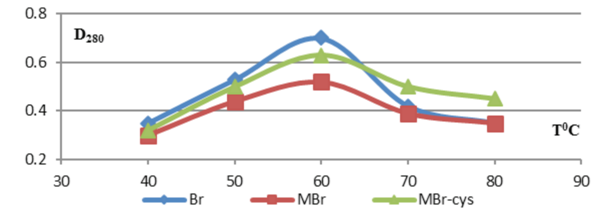

Fig 3. Dependence of proteolytic activity on temperature. t - native bromelain (Br), n - modified bromelain (MBr), - modified bromelain with cysteine (MBr-Cys). y -axis: optical density; x – axis: temperature ˚C during proteolytic activity measurement; values represent the average of triplicate measurements

Taking into consideration the obtained results and comparing them with literary data we suggest that modified bromelain will have much potential in medical application than currently available native product. Further research is required to test the effect of this modification on bromelain’s specific pharmacological and allergic properties.

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SUMMARY

CHEMICAL MODIFICATION OF BROMELAIN WITH DEXTRAN ALDEHYDE AND ITS POTENTIAL MEDICAL APPLICATION

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The aim of this study was to obtain a more stable and less allergic form of bromelain, an enzyme complex derived from the stem of Pineapple plant (Ananas comosus L. Merr.), via chemical modification with a polysaccharide. In order to obtain purified bromelain (enriched with protein) from comercial bromelain, protein precipitation method by alcohol was used. According to our results the protein concentration after the purification was increased by about 20%. In this work, we examine the method of bromelain's chemical modification with a water-soluble, biocompatible and biodegradable natural polysaccharide – dextran, oxidized to dextran aldehyde. For the determination of the degree of bonding gel-filtration of bromelain and modified bromelain on sephadex G-75 was performed. After gel filtration of bromelain only one fraction-peak was obtained, whereas after gel filtration of modified bromelain with dextran two fraction-peaks were obtained and the degree of protein bonding with dextran was 65±5%. The method was developed both with and without the addition of cysteine. The addition of cysteine increased the activity of modified bromelain from 50±5% to 70±5%. the pH optimum for native bromelain was 7.5, whereas for modified bromelain it was shifted towards 8.5, while the temperature optimum in both cases was 60˚C.

Taking into consideration the obtained results and comparing them with literary data we suggest that modified bromelain will have much potential in medical application than currently available native product. Further research is required to test the effect of this modification on bromelain's specific pharmacological and allergic properties.

Keywords: Bromelain; enzyme; modification; dextran aldehyde.

РЕЗЮМЕ

ХИМИЧЕСКАЯ МОДИФИКАЦИЯ БРОМЕЛАИНА ДЕКСТРАН АЛЬДЕГИДОМ И ЕГО ПОТЕНЦИАЛЬНОЕ МЕДИЦИНСКОЕ ПРИМЕНЕНИЕ

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Целью исследования явилась разработка более стабильной и менее аллергической формы бромелаина, ферментного комплекса, получаемого из стеблей ананаса (Ananas comosus L. Merr.) путем химической модификации полисахаридом. Для получения очищенного бромелаина, обогащенного белком, из коммерческого бромелаина использовался метод осаждения белка спиртом. Согласно полученным результатам, концентрация белка после очистки увеличилась примерно на 20%. Исследован метод химической модификации бромелаина водорастворимым, биосовместимым и биоразлагаемым природным полисахаридом - декстраном, предварительно окисленным до декстран альдегида. Для определения степени связывания проведена гель-фильтрация на сефадексе G-75. После гель-фильтрации бромелаина получен только один фракционный пик, тогда как после гель-фильтрации модифицированного бромелаина с декстраном получены два фракционных пика, и степень связывания белка с декстраном составила 65±5%. Метод разработан как с добавлением цистеина, так и без него. Добавление цистеина увеличило активность модифицированного бромелаина с 50±5% до 70±5%. Оптимум pH для нативного бромелаина составил 7.5, тогда как для модифицированного бромелаина он сдвинулся в сторону 8.5, а температурный оптимум модифицированного бромелаина оставался аналогичным нативному бромелаину и составил 60^0C.

Принимая во внимание полученные результаты и сравнивая их с литературными данными, авторы предполагают, что модифицированный бромелаин будет иметь больший потенциал для медицинского применения, чем доступный в настоящее время нативный продукт. С целью проверки влияния этой модификации на специфические фармакологические и аллергические свойства бромелаина необходимо проведение дальнейших исследований.

რეზიუმე

ბრომელაინის ქიმიური მოდიფიკაცია დექსტრან ალდეჰიდით და მისი პოტენციური სამედიცინო გამოყენება

[1]თ.კორინთელი, [2]ნ.გორგასლიძე, [1]ლ.ნადირაშვილი, [1]გ.ერქომაიშვილი

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, [1]იოველ ქუთათელაძის ფარმაკოქიმიის ინსტიტუტი; [2]სოციალური და კლინიკური ფარმაციის დეპარტამენტი, საქართველო

კვლევის მიზანი იყო მცენარე ანანასის (Ananas comosus L. Merr.) ღეროსგან მიღებული ფერმენტების კომპლექსის - ბრომელაინის პოლისაქარიდთან ქიმიური მოდიფიკაციით უფრო სტაბილური და ნაკლებად ალერგიული ფორმის მიღება. კომერციული ბრომელაინისგან გასუფთავებული ბრომელაინი (ცილით გამდიდრებული) მიღებულია სპირტით დალექვის მეთოდის გამოყენებით. შედეგად, ცილის კონცენტრაცია გაიზარდა 20%-ით.

შესწავლილია ბრომელაინის ქიმიური მოდიფიკაციის მეთოდი წყალში ხსნადი, ბიოშეთავსებადი და ბიოდეგრადირებადი ბუნებრივი პოლისაქარიდით, დაჟანგული დექსტრანით, დექსტრან ალდეჰიდით. შეკავშირების ხარისხის განსასაზღვრად, გელ-ფილტრაცია ჩატარდა სეფადექს G-75-ზე. ბრომელაინის გელ-ფილტრაციის შედეგად მიღებულია მხოლოდ ერთი ფრაქცია-პიკი, ხოლო დექსტრანით მოდიფიცირებული ბრომელაინის გელ-ფილტრაციის შედეგად – ორი. ცილის დექტრანთან შეკავშირების ხარისხი შეადგენდა 65±5%-ს. მოდიფიკაციის მეთოდი შემუშავდა ორი გზით, ცისტეინის დამატებით და მის გარეშე. ცისტეინის დამატების შემთხვევაში, მოდიფიცირე-

ბული ბრომელაინის აქტივობა გაიზარდა 50±5%-დან 70±5%-მდე. მოდიფიცირებული ბრომელაინის pH-ის ოპტიმუმმა 7.5-დან გადაინაცვლა ტუტე არისკენ და გახდა 8.5, ხოლო ტემპერატურული ოპტიმუმი ნატიურის მსგავსად დარჩა 60^0C.

მიღებული შედეგების გათვალისწინებით და მათი შედარებით ლიტერატურულ მონაცემებთან, ავტორები გამოსთქვამენ ვარაუდს, რომ ამჟამად არსებულ ბუნებრივ პროდუქტთან შედარებით, მოდიფიცირებულ ბრომელაინს მედიცინაში გამოსაყენებლად გააჩნია გაცილებით დიდი პოტენციალი. ბრომელაინის სპეციფიკურ ფარმაკოლოგიურ და ალერგიულ თვისებებზე მოდიფიკაციის ეფექტის შესამოწმებლად საჭიროა დამატებითი კვლევების ჩატარება.

MILESTONES AND PITFALLS IN STRATEGIC PLANNING OF HEALTHCARE IN CAPITAL CITY IN TRANSITION

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Strategic planning plays an important role in the sustainable functioning and development of any authority [1]. Strategic planning is frequently applied at all levels of public and private organizations, including hospitals, demonstrating high results for the better performance of such organization or governmental authorities [2-4]. Strategic planning can be applied as effective instrument for the sustainable growth, which could also be applied in the healthcare system [5]. A study from high-income countries demonstrated high role of strategic planning, whereas studies from the middle and middle-low income countries reported formal approach for the strategic planning in the public sector, including healthcare. This is resulted in the low achievements of the strategic goals, indicating bad planning. The possible cause of the formal strategic planning is low understanding from the leadership of role of strategic planning, low control form the higher levels of authorities. Ukraine is balanced between the middle and middle-low income positions. The capital of Ukraine is Kyiv (also known as Kiev), it is also largest economic and political center of the country. Ukraine and its cities, including Kyiv, are currently in transition, due to unstable economy of Ukraine, poverty, corruption as well as ongoing hybrid warfare in the East of country, affecting also financing of healthcare system [6-12]. Still, since the independence in 1991, government of Ukraine has been attempting to improve the country by reforming all sectors of the state [12,13]. These attempts have been also associated with the adoption of strategic plans for Ukraine since 2001, but achievements from that plans was not fully evaluated. The current strategic plan of Ukraine was adopted in the 2015, whereas Kyiv strategic plan was adopted in 2011, but significant changes were made in 2019 in order to follow the major goals of the country. Health is an important indicator of the any state, because it part of human capital, playing an important role in the economic stability and sustainability. The strategy plan for country and city performance is an important tool to achieve the best results for the sustainable development during ongoing transition processes in economics, demonstrating a significant impact on the human health. The aim of this study was to investigate and evaluate implementation of strategic plan for Kyiv with the focus on healthcare sector.

Material and methods. Adopted documents were obtained from the official electronic recourses of the Kyiv city administration and city's Department of Healthcare. There were identified such documents as Strategic plan for Kyiv for period 2011-2020, concept for healthcare development from the Department of Healthcare, City's target program "Health of Kyivers", in which Kyivers means citizens of Kyiv. Out of these documents, Strategic plan for Kyiv is the major one, whereas concept from city's Department of Healthcare is considered as a backstop for the strategy of healthcare. City target program "Health of Kyivers" is aimed to provide financing from budget of Kyiv for the various healthcare-related projects under supervision from the city's Department of Healthcare. Therefore, both concept for healthcare development of city's Department of Healthcare and City target program "Health of Kyivers" are strongly associated with the health-related goals in the Strategic plan for Kyiv. These documents were analyzed concerning their matching to the part of healthcare planning, and strategic goals status was evaluated from the official annual reports. Statistical analyses were performed by GraphPad Software. Categorical variables were evaluated by Fisher's exact test (two-tailed) and p value less that 0.05 was considered as significant.

Results and discussion. Analyses of Ukrainian Laws and other legal documentation from the governmental authorities revealed multiple documents regulating strategic planning in Ukraine. It is obligatory for regional government and cities administrations to adopt strategic plan, to follow it and to report its results. Our analyses showed, that both reports of the strategic and operational performance of government authorities are regulated by the resolution from the Cabinet of Ministers of Ukraine (11.11.2015 № 932), which is not in line with Baldridge model for self-assessment. Kyiv's strategic plan was adopted in 2011, followed by its update in the 2015 due to changes in the Ukrainian legislation [8, 13]. The strategic plan of Kyiv is valid for 10 years from 2015 to 2025. Department of Healthcare of Kyiv is a local administrative authority for management of