# ТЕХНОЛОГІЯ ВИРОБНИЦТВА І ПЕРЕРОБКИ ПРОДУКЦІЇ ТВАРИННИЦТВА

*Збірник наукових праць*

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# CONTENT

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# The use of agricultural production waste in relation to bio nano technology for the synthesis of functionalized selenium nanoparticles

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Бітюцький В.С., Цехмістренко С.І., Демченко О.А., Цехмістренко О.С., Мельниченко О.М., Олешко О.А., Мельниченко Ю.О. Використання відходів сільськогосподарського виробництва у біонанотехнології синтезу функціоналізованих наночастинок селену. Збірник наукових праць «Технологія виробництва і переробки продукції тваринництва», 2022. № 2. С. 42–50.

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The application of nanotechnological innovations to increase the effectiveness of the bioflavonoid quercetin is considered. The ability to functionalize with specific ligands that target specific organs or cells is very important because it is possible to increase the concentration of quercetin at the desired target level while reducing side effects. Quercetin, as a flavonoid antioxidant, is widely used to reduce oxidative stress and activate important signalling pathways in cells. However, poor solubility in water, intensive first-pass metabolism limits its use. A strategy for the development of nanocomposites is presented, which involves combining quercetin obtained from agricultural waste with selenium nanoparticles. In vitro results demonstrated that quercetin-nanoselenium has high water solubility compared to individual flavonoids. It has been proven that quercetin-nano-selenium nanoparticles are capable of reducing 1,1-dipheny l-2-picrylhydrazyl (DPPH) radicals and are characterized by high antioxidant activity. The ability to functionalize nanoparticles with specific ligands that target the modulation of specific signaling pathways (Keap1/Nrf2/ARE, Nf-kB, mTOR) in individual cells is very important, as it allows increasing the concentration of quercetin to the desired level while reducing side effects.

Considering the beneficial effects of quercetin, a strategy has been developed that involves the use of selenium nanoparticles to deliver quercetin in a specific and controlled manner. Research in this direction is promising, as it will contribute to clarifying the expediency of using such nanosystems, which have not yet been widely used. The use of onion waste and its extracts in biotechnology, biomedicine, pharmaceuticals and the agro-industrial sector can be an optimal solution for reducing environmental damage. In addition, it will provide an economically determined alternative for the production of feed additives for animals and poultry. Compounds of quercetin with nanoselenium should take a worthy place in clinical medical practice, biology and agriculture. The beneficial effects of quercetin can be further enhanced with the help of nanotechnology, which will contribute to the effective use of this compound with such great biological potential.

**Key words:** nanobiotechnologies, waste, onion peel, 1,1-dipheny l-2-picrylhydrazyl, antiradical activity.

**Introduction.** Bionanotechnology emerged as an integration of biotechnology and nanotechnology for the development of biosynthetic and environmentally safe technologies for the synthesis of nanomaterials, and "green" synthesis and surface modification of nanoparticles are crucial in this field [34]. Nanoparticles (NPs), synthesized using plant extracts or phytocomponents, are of great importance in the development of various therapeutic and diagnostic tools [30]. Biogenic, "green" synthesis of metal nanoparticles, metal oxides and metalloids with the participation of plants and microorganisms combines biological principles with biochemical approaches to obtain nano-sized functional particles with the necessary properties. Environmental cleanliness of the production of nanostructures, the use of which is growing at a significant rate, is an urgent problem today. The advantages of further synthesis by biological means, i.e. using microorganisms (yeast, fungi, bacteria) and plant parts (stem, root, leaves, bark, flowers, etc) include non-toxicity, easy reproducibility and economic efficiency [5, 40, 41].

Various strategies and biomodifiers are used for surface modifications/functionalization of these nanomaterials, in particular with the participation of flavonoids. Flavonoids are one of the most widespread classes of compounds found in vegetables and fruits. Flavonoids are divided into classes, and although structurally unique, they share a common core structure formed by three rings known as the flavan core. The position of the hydroxyl group (–OH) in one of the rings determines the mechanisms of action of flavonoids and reveals complex multifunctional activity. Flavonoids are widely used as antioxidants, analgesics, and anti-inflammatory agents, showing safe preclinical and clinical profiles [16]. Flavonoids are divided into classes: flavones (flavone, apigenin, and luteolin), flavonols (quercetin, kaempferol, myricetin, and fisetin), and flavanones (flavanone, hesperetin, and naringenin).

Quercetin (Q) (3,3',4',5,7-pentahydroxyflavone) is a flavonol found in various types of fruits, vegetables, and plants, including: berries, apples, tomatoes, cocoa, onions, and certain medicinal plants [17, 27].

The properties of quercetin as a dual-acting antioxidant are due to its ability to act as a direct antioxidant, removing active forms of oxygen and nitrogen. These highly reactive ions are formed during metabolic processes or come from exogenous sources such as pollution, radiation, etc In addition, quercetin may act as an indirect antioxidant by activating the Nrf2 signaling pathway and the transcription of antioxidant enzymes.

Quercetin is an antioxidant flavonoid that exhibits anti-inflammatory activity due to the inhibition of pro-inflammatory cytokines [18], oxidative stress [6, 7, 9, 42], NLRP3 inflammasome activity in macrophages [13], activation of p65 NF-κB [19, 26], MAP kinase signaling in macrophages [26], p50 NF-κB activation in primary human keratinocytes [44], and TNF-α, IL-1β, and IL-6 production in LPS-stimulated cells [10]. In addition to the inhibition of the above-mentioned pro-inflammatory signaling pathways, part of this effect is carried out due to the activation of the Nrf2/ HO-1 pathway [7, 19]. Quercetin can activate the AMPK pathway to modulate mTOR in a dose-dependent manner and contribute to the reduction of nuclear translocation of NF-κB to inhibit pro-inflammatory processes [8].

However, poor water solubility and intensive first-pass metabolism limit the clinical use of quercetin. It was found that selenium nanoparticles conjugated with quercetin inhibit the aggregation of amyloid-β structures, which are a sign of Alzheimer's disease, and exhibit antioxidant properties. Such nanocomposite carriers significantly increase water solubility and bioavailability of quercetin (QNPSe) [37].

Biological synthesis is one of the most environmentally friendly methods of synthesis of nanostructures. Moreover, if the synthesis is carried out with the help of waste, in particular plants, then the synthesis process not only becomes green, but also environmentally friendly. Onion husks are one of these vegetable wastes. In the case of onion processing at the domestic or industrial level, a large amount of waste is generated, including unfit for food: the upper and lower parts, the outer skin and two outer layers [12]. It is reported that among all producers, only European countries can generate almost 0.6 million tons of onion waste annually [23]. In addition, these wastes can have a harmful effect on the environment if not properly disposed of, as they are not suitable for making feed, nor can they be used as fertilizer [2]. Therefore, onion waste remains underutilized even after establishing the fact that it is a rich source of bioactive compounds such as phenols, flavonoids, and flavanols. Thus, increasing the value of onion waste and its extracts in the field of biotechnology, biomedicine, pharmaceuticals and the agro-industrial sector can be an optimal solution to reduce environmental damage and provide an economical, inexpensive alternative for the production of medical supplements or drugs [24].

Onion husks are considered to be waste, which is detected 20 times more quercetin and glycosides of quercetin than the edible part [25]. It is believed that onions have numerous phytochemicals, flavonoids and enzymes that help in the synthesis of nanoparticles [24].

Despite the differences in varieties or extraction methods, the main phenolic compound identified in onions is quercetin. The identified compounds included quercetin 4'-o-glucoside and quercetin, as well as other quercetin glycosides, cyanidine 3-O-glucoside and a number of degradation products and oxidation of quercetin [24].

Quercetin has a protective effect on cancer and cardiovascular diseases, chronic inflammation, oxidative stress and neurodegenerative pathology due to its anti-radical and anti-inflammatory properties, however, its poor bioavailability inhibits the potential beneficial effects of this flavonoid. In this sense, different types of nanosis have been developed to improve quercetin solubility, as well as to develop fabric-specific delivery systems. These studies allow you to improve the bioavailability of quercetin and increase its concentration in the right places. Thus, quercetin can become a promising compound if you use nanotechnology as a tool for improving its therapeutic efficacy [33].

Instead of using commercially affordable but expensive quercetin, as a stopping agent for the synthesis of gold nanoparticles, researchers [38] used onion husks as a cheap quercetin source, which can act as a strong reducing agent, as well as a calculating agent, and its synergistic. In this work, giving priority to the rational use of natural resources, all the crude onion extract was cleaned up to four fractions, namely: ethyl acetate (EA), butanol, methanol and water [31]. Unlike the use of organic extractants, studies [1] used aqueous onion husk extract in case of green synthesis of silver nanoparticles. Among the various nanostructures of selenium nanoparticles are characterized by unique properties, such as high catalytic and biological activity, and biogenic selenium nanoparticles obtained by "green" chemistry methods, affect the redox-sensitive Keap1/NRF2/are different stressful effects by activating transcription and synthesis of a number of antioxidant and detoximizing enzymes [4]. Quercetin has been proven to counteract neuro-steaming by activating NRF2/HO-1 and inhibiting the transmission of NF-KB signals [39]. Thus, the functionalization of selenium nanoparticles can contribute to the effects of nanocomposition on transcription factors NRF2 and NF-KB, key pathways that regulate the subtle balance of cellular oxidative status and response to stress and inflammation. Our studies are aimed at synthesis of nanobioconjugates selenium with quercetin for the use of water extract of onion husk, which is a waste of agro-industrial production.

**The aim of the research** is studying the process of synthesis of functionalized flavonoids of selenium nanoparticles for the use of water extract of onion husk, research of radical-absorbent activity of nanobioconjiangists of selenium.

**Material and methods of research.** Onion (Allium cepa L), widely known as common onion, belongs to the Amaryllidaceae family. Onion husks were used as a source of flavonoids for the preparation of functionalized selenium nanoparticles. The onion husks were washed several times with distilled water to remove dust and dirt on it, and dried in the air. The dried vegetable raw material was crushed and sifted through a sieve and placed in the extractor. The extraction was carried out in the ratio of raw materials: extractant - 1:25 at extraction temperatures 90 °C for 15 minutes. Water was purified as extractants. In the event of extraction, the extracts were filtered through filter paper. For the preparation of selenium nanoparticles as a stabilizing factor and the reducing agent used fresh extract made from onion husk. 50 ml of filtrate was taken for synthesis of nanoparticles (NPs). Selenium nanoparticles (SeNPs) were performed as follows: 200 ml of 10 mm of sodium selenite ($Na_2SeO_3$) were dissolved by the precursor in distilled water and added drops of onion husk extract with constant mixing to change the color of the reaction mixture. The solution was left in mixing conditions for 3 hours after the incubation time confirmed the synthesis of the SeNPs. UV- and visible spectra of functionalized selenium nanoparticles were recorded in various chronological intervals (1 hour, 2, 3 hours). Antioxidant (radical-absorbent) activity of synthesized nanoslenium compounds was determined by the method based on the ability of antioxidant molecules of the test substance to restore free radical radicals 2.2-dipheny l-1-1-pyxilhydrazil (DPPH). DPPH is a stable free radical, the solution of which is purple. The DPPH solution (0.4 mm in 80 vol. The absorption was measured at 517 nm using a spectrophotometer [46].

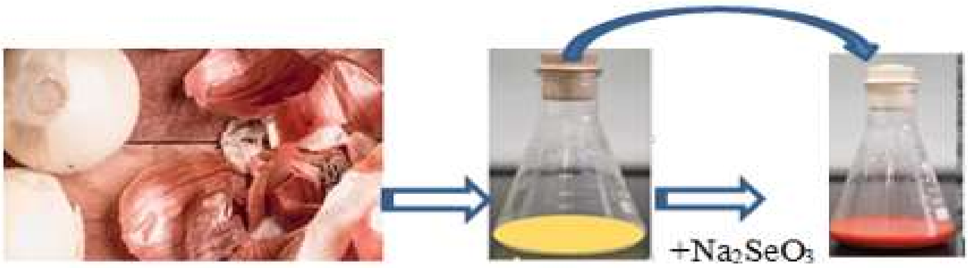
**Results and discussion.** Selenium nanoparticles obtained from onion husks, which were discarded as biowaste in landfills, were used as the object for this study.

The reduction of sodium selenite to zero-valent selenium was monitored using a UV-visible spectrophotometer, and the presence of a strong surface plasmon resonance, a characteristic phenomenon exhibited by selenium nanoparticles, confirmed the presence of nanoselenium in the medium.

Visual coloring is the first stage of research into the process of selenium nanoparticle formation. At the first stage of the reaction, the color of the mixture was yellow, which gradually changed to red-brown over time (Fig.1). After 3 hours of incubation, no further color changes were observed. The appearance of a red-brown color is caused by the excitation of plasma resonance surface oscillations by selenium nanoparticles, which provides spectroscopic evidence of their formation. Analysis of the spectrum showed an absorption peak at λ=370 nm, which confirms the formation of selenium nanoparticles.

The acquired color can also reveal the morphology of the nanoparticles, as red solutions tend to be monocyclic or amorphous (spherical), while dark and black solutions tend to be triangular, linear, or rod shaped [14, 22]. The height of the absorption peak increased with time, but no further increase in its intensity was observed after 3 hours of reaction, which indicates the maximum transformation of $SeO_3^{2-}$ into $Se^0$. (Fig. 2). As a result of the conducted research, a pronounced radical-absorbing effect of nanoselenium conjugates with phenolic compounds from aqueous extracts of the husk was established, compared to the standard – a quercetin solution. Quercetin showed its properties as a reducing agent by 72,4 %, and nanoselenium conjugates reduced DPPH radicals by DPPH on 86,7 %.

DPPH is a compound that contains a nitrogen radical in the centre and has a deep purple colour in ethanol solution. It was established that in the presence of conjugated selenium nanoparticles with flavonoids (QSeNPs) from onion peel, the color of the DPPH solution gradually changes from intense purple to light yellow, which corresponds to the transition of DPPH into a non-radical form (Fig. 3). The evolution of the reaction was observed by analysing the UV-visible spectroscopy at the absorption peak at λ=517 nm (characteristic UV-visible peak of DPPH) in the presence of the QSeNPs catalyst.




Onion peel Extract QSeNPs

Fig.1. **Synthesis of nanobioconjugates of selenium and quercetin using aqueous onion peel extract.**

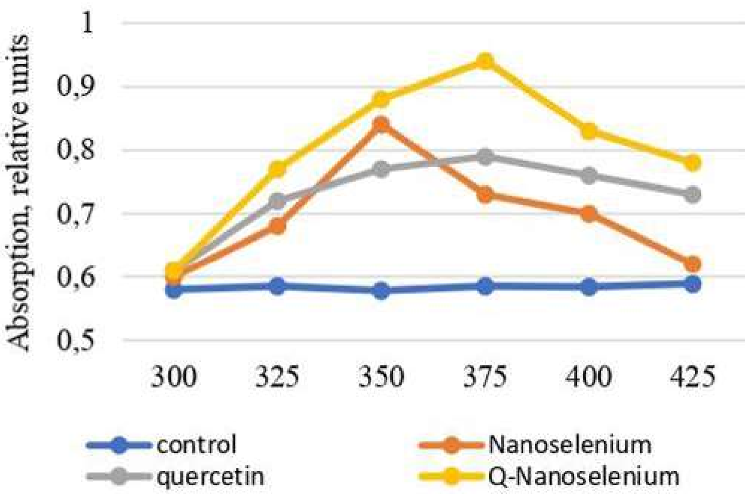
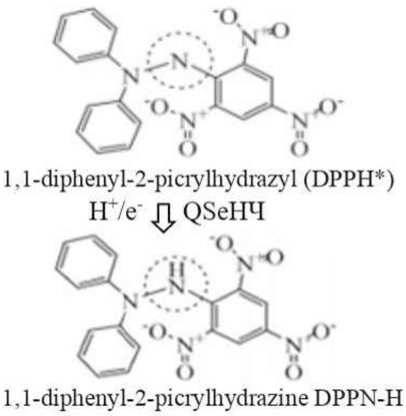



Fig. 2. **Absorption spectra of selenium nanoparticles and conjugates of nanoselenium with quercetin (QSeNPs).**

Fig. 3. **Conversion of 1,1-diphenyl-2-picrylhydrazyl (DPPH*) to 1,1-diphenyl-2-picrylhydrazine DPPN-H by quercetin-nanoselenium (QSeNP) conjugates and color change from purple to light yellow.**

The colour change occurs due to the conversion of 1,1-diphenyl-2-picrylhydrazyl (DPPH*) into 1,1-diphenyl-2-picrylhydrazine DPPN-H by quercetin-nanoselenium conjugates (QSeNPs). The reaction proceeds according to the scheme:




Thus, the obtained selenium nanoconjugates show high anti-radical activity against DPPH* due to their hydrogen/electron transfer ability.

Numerous studies, conducted mainly in vitro, show that flavonoids can be classified as non-enzymatic antioxidants capable of directly or indirectly attenuating or preventing cell damage caused by free radicals [36].The antioxidant properties of many flavonoids are much stronger than those of vitamins C and E [35].

Flavonoids can prevent cell damage caused by free radicals by various mechanisms (Fig. 4).

The mechanism of free radical binding by flavonoids was proposed and supported by a number of researchers for the first time in the form of a hypothesis [32, 36]. The proposed hypothesis includes three main targets (Fig. 5).

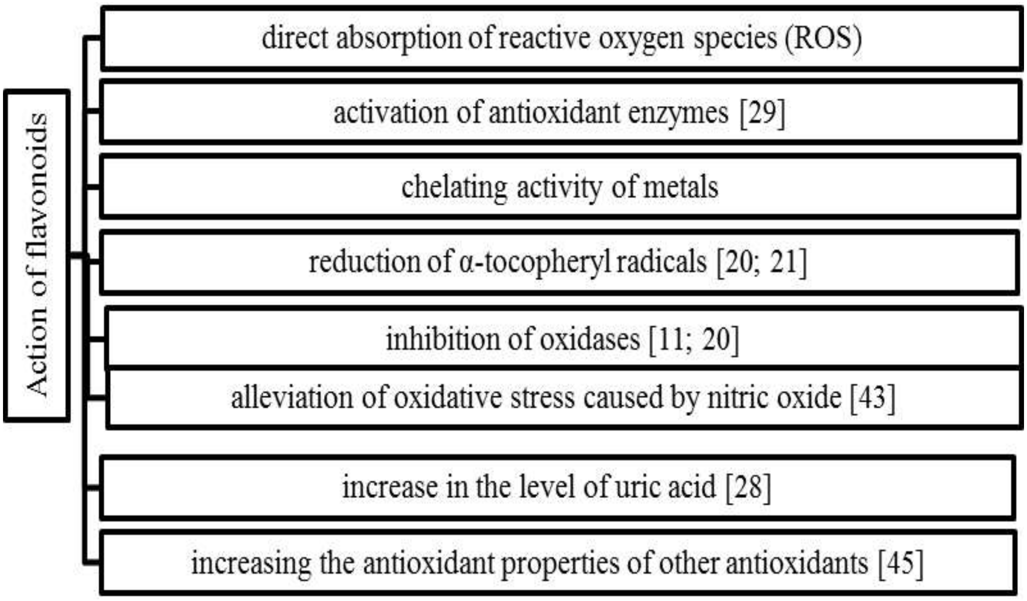



Fig. 4. **Main metabolic pathways of flavonoids action.**

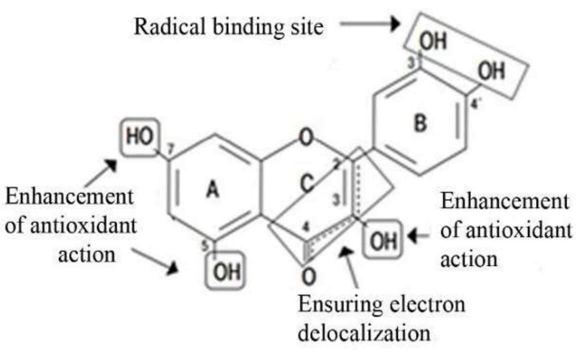



Fig. 5. **The main targets in the flavonoid molecule (using the chemical structure of quercetin as an example) that ensure the binding of free radicals (adapted from [6]).**

1) Hydroxyl groups 3´and 4´ associated with ring B (catechal structure) are the main characteristic of flavonoids, necessary for "quenching" free radicals. At the same time, the hydroxyl groups in the B-ring probably play the most important role in the sequencing of reactive oxygen species (ROS), while similar substituents in the A rings have a much lower antioxidant effect.

2) The double bond 2, 3 in conjugation with the 4-oxo-(ketone)-group in ring C provides electron delocalization from ring B. Electron delocalization of aromatic rings is known to stabilize the formed radicals (probably due to resonance) when flavonoid interacts with RFK.

3) Hydroxyl groups connected to rings A and C in the 3rd, 5th and 7th positions, together with the 4-oxo group, also increase the antioxidant activity of flavonoids, probably ensuring hydrogen bonding with the oxo group.

In vitro experiments have established that flavonoids, which are characterized by all the noted features of the chemical structure, have the greatest ability to inactivate free radicals. Such polyphenols include the flavonols quercetin and myricetin, as well as flavan-3-oleepicatechinagalate, epigallocatechin and, especially, epigallocatechin gallate. At the same time, a significant role in increasing antiradical activity is played by the hydroxyl group in position 3, which brings additional activity to flavonols and flavan-3-ols [36].

**Conclusion.** The paper presents an innovative "green" synthesis of quercetin-functionalized selenium nanoparticles using onion peel extract, which allows the use of biological waste for the preparation of environmentally friendly nanoconjugates. The presented bionanotechnology is effective, environmentally safe, economically attractive and allows obtaining stable composite selenium nanoparticles. Selenium nanoparticles, functionalized with quercetin, synthesized from agricultural waste (onion husks), are biocompatible, have antioxidant / antiradical properties and can be included in feed additives for animals and poultry.

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**Використання відходів сільськогосподарського виробництва у біонанотехнології синтезу функціоналізованих наночастинок селену**

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Розглянуто застосування нанотехнологічних інновацій щодо підвищення ефективності діїбіофлавоноїда кверцетину. Здатність до функціоналізації за допомогою специфічних лігандів, які націлені на певні органи або клітини, дуже важлива, оскільки можна збільшити концентрацію кверцетину на бажаному цільовому рівні, одночасно зменшуючи побічні ефекти.Кверцетин, як флавоноїдний антиоксидант, широко використовується для зменшення оксидативного стресу та активації важливих сигнальних шляхів у клітинах. Однак погана розчинність у воді, інтенсивний метаболізм першого проходження обмежують його застосування. Представлена стратегія розробки нанокомпозитів, яка передбачає поєднання кверцетину, одержаного з відходів сільськогосподарського виробництва, з наночастинками селену. Результати invitro продемонстрували, що кверцетин-наноселен має високу розчинність у воді порівняно з окремими флавоноїдами. Доведено, що наночастинки кверцетин-наноселену здатні довідновлення радикалів 1,1-дифеніл-2-пікрилгідразилу (DPPH) та характеризуються високою антиоксидантною активністю. Здатність функціоналізації наночастинок за допомогою специфічних лігандів, які націлені на модуляцію специфічних сигнальних шляхів (Keap1/Nrf2/ARE, Nf-kB, mTOR) у окремих клітинах, дуже важлива, оскільки дозволяє збільшити концентрацію кверцетину на бажаному рівні, одночасно зменшуючи побічні ефекти.

Зважаючи на сприятливий вплив кверцетину, розроблена стратегія, яка передбачає використан-

ня наночастинок селену для доставки кверцетину специфічним і контрольованим способом. Перспективним є дослідження у цьому напрямку, так як сприятимуть з'ясуванню доцільності використання таких наносистем, які не одержали ще широкого застосування. Використання відходів цибулі та її екстрактів у біотехнології, біомедицині, фармацевтиці та агропромисловому секторі може стати оптимальним рішенням для зменшення шкоди навколишньому середовищу. Окрім того це забезпечить економічно обумовлену альтернативу для виробництва кормових добавок для тварин та птиці. Сполуки кверцетину із наноселеном повинні зайняти достойне місце у клінічній медичній практиці, біології та сільському господарстві. Корисні ефекти кверцетину можуть бути додатково посилені за допомогою нанотехнологій, що сприятиме ефективному застосуванню цієї сполуки з таким великим біологічним потенціалом.

**Ключові слова:** нанобіотехнології, Селен, відходи,лушпиння цибулі, 1,1-дифеніл-2-пікрилгідразил, антирадикальна активність.



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