*REVIEWS, LECTURES*

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# CURRENT STATE OF RESEARCH IN THE FIELD OF CHEMICAL COMPOSITION AND PHARMACOLOGICAL EFFECTS OF *ZEA MAYDIS STYLI CUM STIGMATIS*

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*Zea maydis styli cum stigmatis (*Engl. *corn silk)* are well known in medical practice. In the scientific literature, a lot of information has been accumulated about the chemical composition and pharmacotherapeutic actions of this medicinal plant material. A chronological analysis of this information shows that earlier, the scope of scientific publications was mainly devoted to the study of the choleretic, diuretic, hemostatic kinds of *Zea maydis styli cum stigmatis* activity, and the identification of the active substances responsible for these types of action. Currently, there is a growing scientific interest not only in the individual natural compounds of the *Zea maydis styli cum stigmatis* composition, but also in the search for new aspects of their medical application.

**The aim** of the article is a review and systematization of modern scientific data in the field of the *Zea maydis styli cum stigmatis* chemical composition and their pharmacological action.

**Materials and methods.** For the information and analytical search, the scientific data posted on the following electronic resources were used: PubMed, Web of Science, ScienceDirect, Scopus, Google Scholar, eLibrary. The search was carried out in the period from 2005 to 2021 using the following keywords: *Zea mays* L.; *Zea maydis styli cum stigmatis*; corn silk; chemical composition; pharmacological action.

**Results.** The review is devoted to the generalization and analysis of modern scientific data on the *Zea maydis styli cum stigmatis* chemical composition and their pharmacological action. It has been shown that, as before, the greatest attention of scientists is attracted by flavonoids in the *Zea maydis styli cum stigmatis* chemical composition. Alongside with them, phenolcarboxylic acids, vitamin K, phytosterols, volatile compounds and polysaccharides are of no small importance for the *Zea maydis styli cum stigmatis* pharmacological activity. Modern ideas about the *Zea maydis styli cum stigmatis* pharmacological activity have been expanded by summarizing the study results of their antioxidant, anti-inflammatory, antidiabetic, hypotensive, neuro- and photoprotective activities. The data on the effectiveness of their use as parts of the complex tumor diseases therapy have been published.

**Conclusion.** As a result of the data analysis of modern scientific literature, it has been found out that *Zea maydis styli cum stigmatis* are still in the sphere of scientists' interest. Alongside with the flavonoids of this raw material, other groups of pharmacologically active substances are also being actively studied. It has been revealed that the information about potentially significant and confirmed types of the *Zea maydis styli cum stigmatis* therapeutic action is significantly updated. The results of this review may be useful for identifying promising directions for the development of the drugs based on *Zea maydis styli cum stigmatis*.

**Keywords:** *Zea maydis styli cum stigmatis*; corn silk; chemical composition; pharmachologic action

**Abbreviations:** ZMSS – *Zea maydis styli cum stigmatis*; MPRM – medicinal plant raw material; PASs – pharmacologically active substances; MCF-7 – an epithelial-like cell line derived from invasive human breast ductal adenocarcinoma; TBARS – Thiobarbituric acid reactive substances; mRNA – messenger ribonucleic acid.

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ОБЗОРЫ, ЛЕКЦИИ

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# СОВРЕМЕННОЕ СОСТОЯНИЕ ИССЛЕДОВАНИЙ В ОБЛАСТИ ХИМИЧЕСКОГО СОСТАВА И ФАРМАКОЛОГИЧЕСКОГО ДЕЙСТВИЯ КУКУРУЗЫ СТОЛБИКОВ С РЫЛЬЦАМИ (ОБЗОР ЛИТЕРАТУРЫ)

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Кукурузы столбики с рыльцами (КСР) (лат. – *Zea maydis styli cum stigmatis,* англ. – *corn silk)* хорошо известны в медицинской практике. В научной литературе накоплено немало информации о химическом составе и фармакотерапевтическом действии данного лекарственного растительного сырья. Хронологический анализ этих сведений показывает, что ранее ландшафт научных публикаций был посвящен, главным образом, изучению желчегонной, диуретической, кровоостанавливающей активности КСР и выявлению действующих веществ, ответственных за данные виды активности. В настоящее время отмечается нарастающий научный интерес не только к отдельным индивидуальным природным соединениям в составе КСР, но и к поиску новых аспектов их медицинского применения.

**Цель.** Обзор и систематизация современных научных данных в области химического состава и фармакологического действия КСР.

**Материалы и методы.** Для информационно-аналитического поиска использовали научные данные, размещенные на электронных ресурсах PubMed, Web of Science, ScienceDirect, Scopus, Google Scholar, eLibrary. Поиск осуществляли за период с 2005 г. по 2021 г. по ключевым словам: кукуруза обыкновенная; кукурузы столбики с рыльцами; *Zea maydis styli cum stigmatis; corn silk;* химический состав; фармакологическое действие.

**Результаты.** Обзор посвящен обобщению и анализу современных научных данных о химическом составе и фармакологическом действии КСР. Показано, что по-прежнему наибольшее внимание ученых в составе КСР привлекают флавоноиды. Наряду с ними немаловажное значение для фармакологической активности КСР имеют фенолкарбоновые кислоты, витамин К, фитостерины, летучие соединения и полисахариды. Современные представления о фармакологическом действии КСР расширены за счет обобщения результатов исследования их антиоксидантной, противовоспалительной, антидиабетической, гипотензивной, нейро- и фотопротекторной активности. Опубликованы данные, свидетельствующие об эффективности их применения в составе комплексной терапии опухолевых заболеваний.

**Заключение.** В результате проведенного анализа данных современной научной литературы было установлено, что интерес ученых к КСР не ослабевает. Наряду с флавоноидами данного сырья достаточно активно изучаются и другие группы фармакологически активных веществ. Выявлено, что существенно обновились сведения о потенциально значимых и подтвержденных видах лечебного действия КСР. Результаты данного обзора могут быть полезны для определения перспективных направлений разработки лекарственных средств на основе КСР.

**Ключевые слова:** кукурузы столбики с рыльцами; *Zea maydis styli cum stigmatis, corn silk;* химический состав; фармакологическое действие

**Список сокращений:** КСР – кукурузы столбики с рыльцами; ЛРС – лекарственное растительное сырье; ФАВ – фармакологически активные вещества; MCF-7 – эпителиоподобная клеточная линия, полученная из инвазивной аденокарциномы протоков молочной железы человека; ТБК-АП – активные продукты, реагирующие с тиобарбитуровой кислотой; мРНК – матричная рибонуклеиновая кислота.

## INTRODUCTION

Medicinal plant drugs do not only remain relevant, but are increasingly becoming objects of research by scientists from around the world. On the one hand, this trend is quite naturally based on a combination of the historically proven effectiveness of their use, and, on the other hand, it is based on a high level of safety in relation to toxic and side effects in comparison with synthetic drugs. In addition, the undoubted advantages of phytopreparations include a mildly increasing effect, often of a multifunctional character, as well as the possibility of using it in patients of various age groups, especially in children and the elderly.

Today, pharmacy and pharmaceutical practice have an extensive arsenal of medicinal plants. At the same time, it should be notified that both new, potentially useful plant sources of pharmacologically active substances (PAS) and those already in demand

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in medical practice, are in the field of researchers' view.

The latter category includes common corn (*Zea mays* L.), which is a producer of a well-known medicinal plant raw material (MPRM) with a pharmacopoeial status of *Zea maydis styli cum stigmatis*, often called corn silk. This raw material is traditionally used as a choleretic, diuretic, and hemostatic agent, due to the rich and diverse *Zea maydis styli cum stigmatis* chemical composition [1].

In the scientific literature, a lot of information has been accumulated about various groups of PASs presented in *Zea maydis styli cum stigmatis*, as well as about the studied and potentially significant types of their pharmacotherapeutic action [2]. A chronological analysis of this information shows that earlier, the scope of scientific publications was mainly devoted to the study of choleretic, diuretic, hemostatic activities of *Zea maydis styli cum stigmatis* and the identification of the active substances responsible for these features [3]. Currently, there is a growing scientific interest not only in the individual representatives of PASs in the *Zea maydis styli cum stigmatis* composition, but also in the study and broadening knowledge about new types of their pharmacotherapeutic action. In particular, within recent years, the results have been obtained and published. They confirmed antioxidant, anti-inflammatory, antidiabetic properties and some other established types of the *Zea maydis styli cum stigmatis* therapeutic action in the extracts and individual PASs obtained from this raw material [4].

Thus, information about the *Zea maydis styli cum stigmatis* biological effect and chemical composition have undergone significant changes. In this regard, it seems relevant to analyze and summarize the scientific information on this issue. The results of such a study, in the authors' opinion, will contribute to the formation of modern ideas about the PAS component composition, the spectrum of its pharmacological activity and the identification of possible prospects for the use of *Zea maydis styli cum stigmatis* to obtain modern effective and safe drugs.

**THE AIM** of the article is a review and systematization of modern scientific data in the field of the *Zea maydis styli cum stigmatis* chemical composition and their pharmacological action.

## MATERIALS AND METHODS

For the information and analytical search, the scientific data posted on the following electronic resources were used: PubMed, Web of Science, ScienceDirect, Scopus, Google Scholar, eLibrary. The search was carried out in the period from 2005 to 2021 using the following keywords: *Zea mays* L.; *Zea maydis styli cum stigmatis*; corn silk; chemical composition; pharmacological action.

## RESULTS AND DISCUSSION

### 1. Zea maydis styli cum stigmatis chemical composition

The *Zea maydis styli cum stigmatis* chemical composition is characterized by a diverse spectrum of PASs. It is represented by phenolic compounds (flavonoids, anthocyanins, and phenolcarboxylic acids), triterpene saponins, organic acids, water- and fat-soluble vitamins, fatty and essential oils, polysaccharides, phytosterols, and some other PASs [5].

#### 1.1. Phenolic compounds

*Zea maydis styli cum stigmatis* phenolic compounds have a fairly representative composition, in which flavonoids are rightfully the most significant. Their role as the most likely carriers of the *Zea maydis styli cum stigmatis* pharmacotherapeutic activity was previously emphasized. Currently, it is confirmed by the requirements of regulatory documentation regarding the quantitative content of compounds of a flavonoid character [4]. According to the literature data, luteolin and apigenin derivatives are considered the predominant *Zea maydis styli cum stigmatis* flavonoids: maisin, methoxymaisin, apimaisin, vitexin, isovitexin, orientin, isoorientin, and a number of others [6–9]. The structural formulas of the main *Zea maydis styli cum stigmatis* flavonoids are shown in Fig. 1.

As for the quantitative content of flavonoids in *Zea maydis styli cum stigmatis*, according to all kinds of sources, it is about 0.5–0.7%, depending on the variety of the maize and its habitat [10–12].

Among the *Zea maydis styli cum stigmatis* flavonoids, the interest of researchers is currently attracted, first of all, by maisin and its analogs isolated from *Zea maydis styli cum stigmatis* and studied by scientists from different countries in relation to the established and potential types of these compounds' pharmacotherapeutic action [13, 14].

Alongside with the compounds of a flavonoid character, the phenolic groups of *Zea maydis styli cum stigmatis* PASs are represented by phenolcarboxylic acids, among which the presence of chlorogenic, ferulic, caffeic and hydroxycinnamic acids was confirmed in the *Zea maydis styli cum stigmatis* composition [3, 15, 16].

According to the scientific literature and the results of the authors' research, *Zea maydis styli cum stigmatis* are quite rich in polyphenolic compounds. In particular, the qualitative composition and the quantitative content of tannins in *Zea maydis styli cum stigmatis* have been studied [3, 17]. Using the method of high performance liquid chromatography, the qualitative composition of the compounds of this group was established, i.e., the presence of gallic, ellagic acids, and a number of other substances [18].

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### 1.2. Vitamins

*Zea maydis styli cum stigmatis* contain a significant amount of compounds of the vitamin origin: vitamins K, group B, ascorbic acid, etc. [2]. At the same time, vitamin K is predominant among the substances of this group.

The presence of vitamin K in the *Zea maydis styli cum stigmatis* composition was established by Prof. Mikhlin in 1941. The scientist was able to isolate a new compound with a vitamin activity from *Zea maydis styli cum stigmatis* and study it in sufficient detail; he called it vitamin $K_3$. The resulting substance was a complex mixture – the lipoid *Zea maydis styli cum stigmatis* fraction obtained as a result of the combined extraction from *Zea maydis styli cum stigmatis*. As a result of the studies, a correlation was notified between the level of chlorophyll content and the concentration of vitamin K3 in *Zea maydis styli cum stigmatis*: the extracts from *Zea maydis styli cum stigmatis* of the immature corn were significantly more active in comparison with those obtained from ripe yellow ones [3].

### 1.3. Polysaccharides

In recent years, the *Zea maydis styli cum stigmatis* polysaccharides have been actively studied. The data on their quantitative content and composition have been obtained and published [19].

The results of the studies on the extraction of this PAS group from *Zea maydis styli cum stigmatis* using enzymolysis and an ultrasonic extraction, the study of their physicochemical and pharmacological properties are presented. It was established that the selected group of PAS consisted of rhamnose, arabinose, xylose, mannose, galactose, and glucose [20, 21].

Two fractions were obtained by acid hydrolysis of the *Zea maydis styli cum stigmatis* polysaccharides, subjected to the studies by gel permeation chromatography, gas chromatography, nuclear magnetic resonance, Fourier transform infrared spectroscopy, scanning electron microscopy. The results showed that the studied polysaccharide fractions consisted of xylose, mannose, galactose, rhamnose, arabinose, and glucose [22].

With the use of 1D and 2D NMR, the structural analysis of the *Zea maydis styli cum stigmatis* polysaccharides showed that their constituents are α-D-glucose, α-L-arabinose, β-D-galactose, β-D-mannose, β-D-xylose, α-L-rhamnose [23].

The results of the studies devoted to the research of the interaction between the *Zea maydis styli cum stigmatis* polysaccharides and flavonoids, are of interest. Using molecular dynamics and thermodynamic modeling, the interaction between polysaccharides with different molecular weights and flavonoids is shown. The authors suggested that the adsorption of flavonoids on polysaccharides can be mainly due to van der Waals forces and hydrogen bonds, and the formation of such complexes can enhance the biological activity of the *Zea maydis styli cum stigmatis* polysaccharides [24].

### 1.4. Saponins

Qualitative reactions and a chromatographic analysis revealed the presence of triterpene saponins (oleanolic and ursolic acids) in *Zea maydis styli cum stigmatis*. In terms of oleanolic acid, the content of this PAS group, determined by using a spectrophotometric method, was about 2.5% on average [3].

### 1.5. Phytosterols

As mentioned above, *Zea maydis styli cum stigmatis* contain phytosterols: β-sitosterol and stigmasterol, which perform important physiological and therapeutic functions. The results of the studies devoted to the search for an effective extraction technology with solvents having different polarity, purification and crystallization of the *Zea maydis styli cum stigmatis* phytosterols using ultrasound, have been published [25].

### 1.6. Volatile compounds

Ion chromatography revealed various volatile *Zea maydis styli cum stigmatis* components with a quantitative predominance of alcohols (2,3-butanediol; ethanol, etc.). Alongside with them, the presence of ketones (2,3-butanedione; 3-hydroxy-2-butanone; 3-methyl-2,5-furandione, etc.), aldehydes (benzeneacetaldehyde; heptanol; hexanol, etc.), furans (furan, 2-pentylfuran, 2,3-dihydrobenzenefuran, etc.) and a number of other compounds, has been established [26].

By gas chromatography and mass spectrometry, the qualitative and quantitative composition of the compounds included in the dichloromethane *Zea maydis styli cum stigmatis* extract, was established by El-Ghorab A. et al. The main constituents of this extract were cis-α-terpineol (24.22%), 6,11-oxidoacor-4-ene (18.06%), citronellol (16.18%), trans-pinocamphone (5.86%), eugenol (4.37%), neo-iso-3-tujanol (2.59%) and cis-sabinene hydrate (2.28%) [27].

### 1.7. Phytohemagglutinins

The *Zea maydis styli cum stigmatis* composition also includes phytohemagglutinins (lectins), which are carbohydrate-protein complexes. The carbohydrate part of the *Zea maydis styli cum stigmatis* lectins is formed by galactose, mannose, glucose, arabinose, xylose. In addition, the traces of rhamnose, uronic acid, glucosamine, galactosamine were found. It has been established that the protein part is represented by asparagine, glutamic acid, glycine, alanine, etc. [3].

Generalized and systematized data on the chemical *Zea maydis styli cum stigmatis* composition are presented in Table 1.

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PHARMACY & PHARMACOLOGY

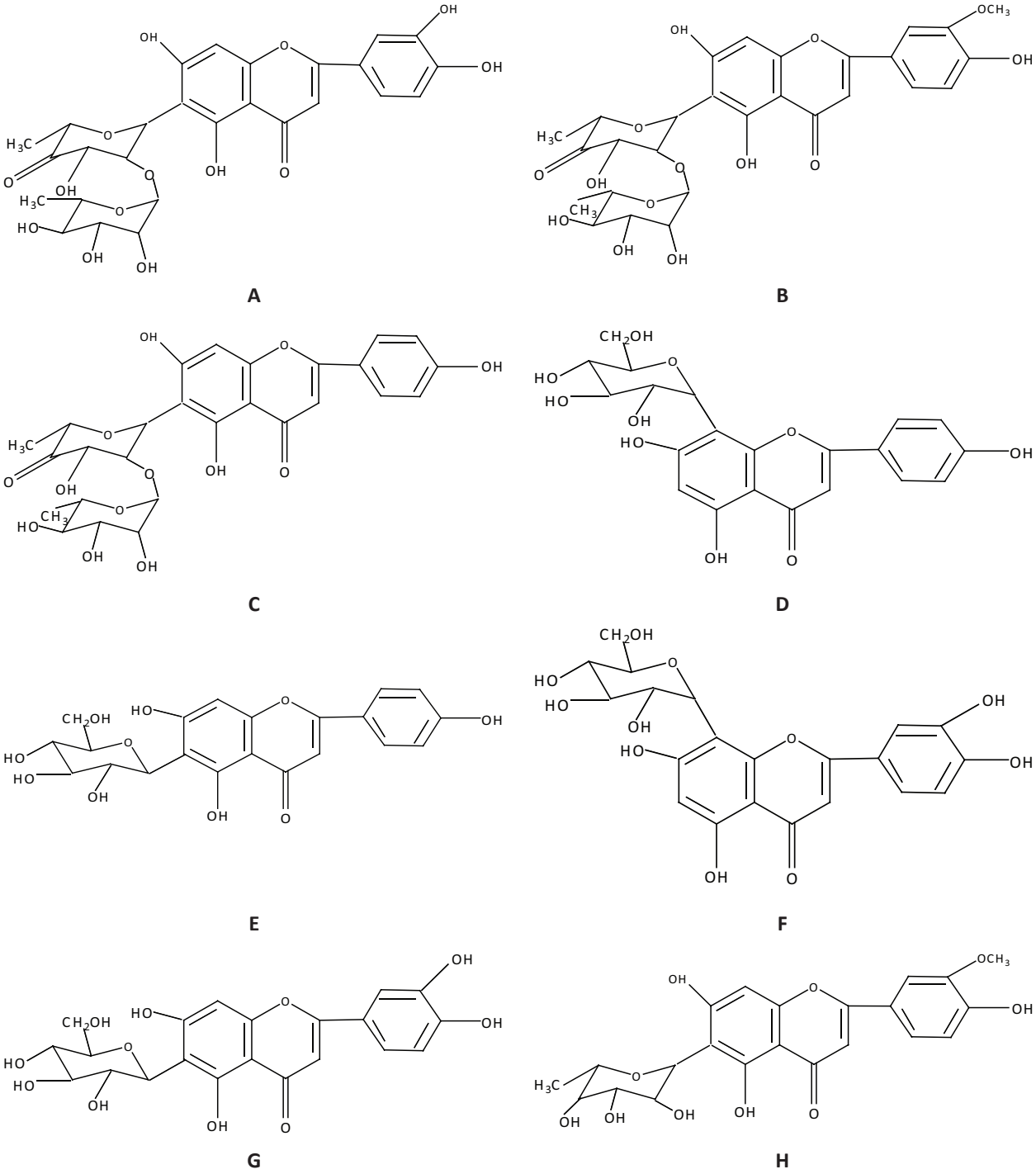


**Figure 1 – Structural formulas of main *Zea maydis styli cum stigmatis* flavonoids**
Note: A – maisin; B – methoxymaisine; C – apimaisin; D – vitexin; E – isovitexin; F – landmark; G – isoorientin; H – chrysoeriol 6-C-β-fucopyranoside.

## 2. Pharmacological action of Zea maydis styli cum stigmatis

### 2.1. Zea maydis styli cum stigmatis application in traditional medicine

The history of the *Zea maydis styli cum stigmatis* application for the treatment of various diseases goes back to the far past. The medicinal properties of *Zea maydis styli cum stigmatis* and a review of the empirical experience of their application are described in sufficient detail by Hager H. in "The Guide to Pharmaceutical and Medico-Chemical Practice", published in 1902–1903. [3, 4].

In folk medicine of various countries, it is recommended to use aqueous extracts from *Zea maydis styli cum stigmatis* most often for the diseases of the liver and biliary tract, kidneys and bladder. In particular, the traditional medicine of China and Japan prefers to use

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**Table 1 – *Zea maydis styli cum stigmatis* chemical composition**

| PAS group | Individual compounds | Source |
|---|---|---|
| Flavonoids<br>Phytohemagglutinins | Maisin, methoxymaisin, apimaisin, chrysoeriol 6-C-β-fucopyranoside; 4''-OH-3'-methoxymaisine molludistin, isomolludistin, vitexin, isovitexin, orientin, isoorientin, isoscoparin, isoquercitrin, quercetin-3,7-diglucoside | [6–14] |
| Phenolcarboxylic acids | Chlorogenic acid, ferulic acid, caffeic acid, hydroxycinnamic acid | [3, 15, 16] |
| Tannins | Gallic acid, ellagic acid, halocatechin, epicatechin, catechin, epigalocatechin, catechin gallate, epicatechin gallate | [3,17, 18] |
| Vitamins | Phylloquinone, thiamine, riboflavin, tocopherol, nicotinamide, ascorbic acid | [2, 3] |
| Polysaccharides | Monomer composition: rhamnose, arabinose, xylose, mannose, galactose, glucose | [20–24] |
| Saponins | Oleanolic acid, ursolic acid | [3] |
| Phytosterols | β-sitosterol, stigmasterol | [25] |
| Volatile compounds | Alcohols: 2,3-butanediol; ethanol; 1,2-propanediol; 2-furanmethanol;<br>ketones: 2,3-butanedione; 3-hydroxy-2-butanone; 3-methyl-2,5-furandio; dihydro-2(3H)-furanone; 2-heptanone; 3-octanone; 2,4-pentanedione;<br>aldehydes: benzeneacetaldehyde, heptanol, hexanol, propanol, pentanol, furfural<br>furan derivatives: furan, 2-pentylfuran, 2,3-dihydrobenzenefuran;<br>terpenoids and phenol derivatives: cis-alpha-terpineol, 6,11-oxidoacor-4-ene, citronellol, trans-pinocamphone, eugenol, neo-iso-3-tujanol, cis-sabinene hydrate | [26, 27] |
| Phytohemagglutinins | Carbohydrate part: galactose, mannose, glucose, arabinose, xylose, rhamnose, uronic acid, glucosamine, galactosamine;<br>protein part: asparagine, glutamic acid, glycine, alanine, lysine, proline, serine, threonine, cysteine, valine, methionine, leucine, isoleucine, tyrosine, phenylalanine, histidine, arginine, cystine | [3] |

a *Zea maydis styli cum stigmatis* decoction as a diuretic [2].

Along with this, folk medicine in Ukraine and Belarus uses *Zea maydis styli cum stigmatis* decoctions for uterine, pulmonary, hemorrhoidal bleeding, edema of the cardiovascular origin, and as a sedative remedy [28]. As a hemostatic agent for gynecological and nasal bleedings, a diuretic for urolithiasis, as well as for the treatment of cholangitis, cholecystitis, hepatitis, atherosclerosis, diabetes, parasitic infestations and obesity, *Zea maydis styli cum stigmatis* decoctions are used in Bulgarian folk medicine [3].

### 2.2. A modern view on the pharmacological action of *Zea maydis styli cum stigmatis*

At the present stage, interest in *Zea maydis styli cum stigmatis* is associated with the research aimed at studying new types of a pharmacological action of this MPRM, detailing the mechanisms of already known and newly discovered therapeutic effects of *Zea maydis styli cum stigmatis*.

#### 2.2.1. Diuretic and nephroprotective action

Thanks to the empirical experience of traditional medicine, diuretic *Zea maydis styli cum stigmatis* actions determined their use at an early stage primarily as a diuretic. Modern researchers could not help being interested in the mechanism of the diuretic *Zea maydis styli cum stigmatis* effect on the kidney function. In particular, *in vivo*, laboratory animals were used to study the excretion of water, uric acid, potassium and sodium ions with urine when taking *Zea maydis styli cum stigmatis* aqueous extracts. It was found out that the *Zea maydis styli cum stigmatis* aqueous extract had a pronounced diuretic effect alongside with a kaliuretic effect. At the same time, a decrease in the glomerular filtration without changing the function of the proximal tubules, the excretion of sodium and uric acid was recorded [29].

*In vivo* studies have shown a positive *Zea maydis styli cum stigmatis* effect on the level of uric acid, which plays a significant role in the pathogenesis and development of cardiovascular diseases complications. The experiments were carried out on several groups of laboratory rats fed with the *Zea maydis styli cum stigmatis* extract, normal food, as well as food with a high salt content, and the *Zea maydis styli cum stigmatis* extract. The determination of the nitric oxide content, superoxide dismutase, glutathione peroxidase and uric acid in the vascular tissues blood of the laboratory animals made it possible to confirm significant negative changes that occurred under the influence of the increased salt intake. Alongside with this, the authors of the study notified that, due to its antioxidant properties, the therapeutic potential of the *Zea maydis styli cum stigmatis* extract may be required in case of an oxidative damage caused by a high salt and/or uric acid content [30].

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Scientific and Practical Journal
PHARMACY & PHARMACOLOGY

**Table 2 – Main types of *Zea maydis styli cum stigmatis* pharmacological action**

| Kind of pharmacological action | Type of study | Object of study | Dose/ concentration | Source |
|---|---|---|---|---|
| Diuretic and nephro-protective actions | *in vivo* | *Zea maydis styli cum stigmatis* aqueous extract | 500 mg/kg | [29] |
| | | *Zea maydis styli cum stigmatis* aqueous extract | 500 mg/kg | [30] |
| | | *Zea maydis styli cum stigmatis* methanolic extract | 200–500 mg/kg | [31] |
| Antihypertensive action | *in vivo* | *Zea maydis styli cum stigmatis* aqueous extract | 130; 192.5; 260 mg/kg | [33] |
| | *in vitro* | *Zea maydis styli cum stigmatis* aqueous extract | 10 mg/kg | [35] |
| Hypoglycemic and antidiabetic actions | *in vivo* | *Zea maydis styli cum stigmatis* aqueous extract | 500 mg/kg | [36, 37] |
| | | *Zea maydis styli cum stigmatis* aqueous extract | 300, 600, 1200 mg/kg | [38] |
| | | *Zea maydis styli cum stigmatis* aqueous extract | 500–4000 mg/kg | [39] |
| | | *Zea maydis styli cum stigmatis* alcohol extract | 100, 300, 500 mg/kg | [40] |
| | | *Zea maydis styli cum stigmatis* polysaccharides | 200, 500, 800 mg/kg | [41] |
| | | *Zea maydis styli cum stigmatis* polysaccharides | 40, 100, 300 mg/ml | [42] |
| | *in vitro* | *Zea maydis styli cum stigmatis* alcohol extract | 50% | [43] |
| | | *Zea maydis styli cum stigmatis* alcohol extract | 5–25 mg/ml | [44] |
| | *in vivo, in vitro* | *Zea maydis styli cum stigmatis* polysaccharides, phenolic compounds | 10 μg/ml | [45] |
| | | *Zea maydis styli cum stigmatis* polyphenolic compounds | 0.001–1 mg/ml | [46] |
| Weight loss, lipid-lowering effect | *in vivo* | *Zea maydis styli cum stigmatis* aqueous extract | 100 mg/kg | [47] |
| | | *Zea maydis styli cum stigmatis* aqueous extract | 100 mg/kg | [48] |
| | | Maisin | 10 mg/kg | [50] |
| | | *Zea maydis styli cum stigmatis* aqueous extract | 600, 800 μg/ml | [51] |
| Antitumor activity | *in vivo* | *Zea maydis styli cum stigmatis* polysaccharides | 50, 100, 200 mg/kg | [53] |
| | | *Zea maydis styli cum stigmatis* alcohol extract | 10 mg/kg | [54] |
| | *in vitro* | *Zea maydis styli cum stigmatis* alcohol extract | 2–10 mg/ml | [55] |
| | | *Zea maydis styli cum stigmatis* methanolic extract | 250, 500, 1000 mg/ml | [56] |
| | | Maisin | 200 μg/ml | [57] |
| | *in vivo, in vitro* | *Zea maydis styli cum stigmatis* polysaccharides | 0–1 mg/ml | [58] |
| Immunotropic action | *in vitro* | *Zea maydis styli cum stigmatis* aqueous extract | 2.5–70 mg/ml | [59, 60] |
| | | Maisin | 100 mg/ml | [61] |
| Anti-inflammatory action | *in vivo* | *Zea maydis styli cum stigmatis* aqueous extract | 1, 2, 4 g/kg | [62] |
| Antioxidant action | *in vitro* | *Zea maydis styli cum stigmatis* alcohol extract | 2% | [28] |
| | | *Zea maydis styli cum stigmatis* methanolic extract | 0.2–4.0 g in simulated medium | [64] |
| Antibacterial action | *in vitro* | *Zea maydis styli cum stigmatis* hexane extract | 1024 mg/ml | [65] |
| Dermatoprotective action | *in vivo* | *Zea maydis styli cum stigmatis* aqueous extract | 2–4 g/kg | [66] |
| | *in vitro* | *Zea maydis styli cum stigmatis* aqueous extract | 0.75–1.5% | [67] |
| | | | 0–1.0 mg/ml | [68] |
| Neuroprotective action | *in vitro* | Maisin | 5–50 mg/ml | [69] |
| | | *Zea maydis styli cum stigmatis* terpens | 25, 50, 100 mmol | [70, 71] |

A study of the *Zea maydis styli cum stigmatis* effect on the *in vivo* gentamicin-induced nephrotoxicity in laboratory rats showed that *Zea maydis styli cum stigmatis* significantly reduced serum creatinine levels. It was found out that under the influence of *Zea maydis styli cum stigmatis*, the manifestations of interstitial nephritis significantly decreased and the occurrence of acute tubular necrosis was not observed, in comparison with the control group of animals. The results obtained showed that *Zea maydis styli cum stigmatis* could reduce the phenomena of nephropathy during a long-term therapeutic use of gentamicin and related aminoglycosides [31].

The results of the herbal medicines study market were published, as a result of which *Zea maydis styli cum stigmatis* were named in the list of top 10 components of herbal medicines for the treatment of the urinary system diseases. It is recommended to use *Zea maydis styli cum stigmatis* as ones of the main components in the development of combined drugs for the treatment of urological and nephrological diseases [32].

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### 2.2.2. Antihypertensive action

In recent years, scientific teams in various countries of the world have been studying antihypertensive effects of *Zea maydis styli cum stigmatis*. In particular, the ability of *Zea maydis styli cum stigmatis* to normalize intraocular and blood pressure has been shown. With this objective in view, a randomized *in vivo* study of the *Zea maydis styli cum stigmatis* aqueous extract effect on these parameters in people suffering from hypertension, was conducted. The results of the experiments showed that therapy with the *Zea maydis styli cum stigmatis* aqueous extract gave a statistically significant dose-dependent decrease in the mean intraocular pressure and blood pressure within a few hours after the administration. According to the authors of the study, the achieved effect may be associated with sodium uresis and diuresis caused by a high content of potassium in the *Zea maydis styli cum stigmatis* extract [33].

Generalized data on the effectiveness of the *Zea maydis styli cum stigmatis* use for the hypertension treatment alone and in combination with synthetic drugs under review, are presented in the published scientific review. The meta-analysis covers five randomized trials involving 567 people, the results of which suggest an increase in the antihypertensive effect when *Zea maydis styli cum stigmatis* is combined with synthetic drugs [34].

The mechanism of the antihypertensive *Zea maydis styli cum stigmatis* action was studied *in vitro* using the methods of proteomics and bioinformatics. The aim of the study was to determine the *Zea maydis styli cum stigmatis* effect on the activity of angiotensine transforming enzyme (ATE) and the presence of components in this MPRM that can have such an effect. The use of proteomics and a bioinformatics analysis made it possible to identify bioactive *Zea maydis styli cum stigmatis* peptides that significantly inhibited the ATE activity and reduced blood pressure levels in a dose-dependent manner. In addition, by means of a docking analysis, the authors showed the interaction mechanism of the discovered peptides with ATE [35].

### 2.2.3. Hypoglycemic and antidiabetic action

As revealed in recent years, alongside with diuretic, choleretic and hemostatic activities, *Zea maydis styli cum stigmatis* have also hypoglycemic properties. The effectiveness of the aqueous *Zea maydis styli cum stigmatis* extract in diabetic nephropathy induced by streptozocin, was studied by Suzuki R. et al. *in vivo.* Urinary albumin excretion and creatinine clearance were studied to diagnose diabetic nephropathy. It was found out that the *Zea maydis styli cum stigmatis* extract prevented glomerular hyperfiltration and suppressed the progression of experimental diabetic glomerular sclerosis. Alongside with that, this group of scientists managed to isolate an individual compound with antidiabetic properties, the structure of which was shown to correspond to chrysoeriol 6-C-β-fucopyranoside. The researchers focused on the advisability of a further *Zea maydis styli cum stigmatis* study in order to expand the prospects for their use in diabetes mellitus and related diseases [36, 37].

The *in vivo* study results of the antidiabetic potential of the *Zea maydis styli cum stigmatis* extract have been published. They indicate that a 4-week application of the extract in laboratory mice significantly increased glucose tolerance and led to a marked decrease in the insulin resistance index. In addition, a decrease in hyperlipidemia, as evidenced by a decrease in total cholesterol, triglycerides, low density cholesterol and an increase in high density cholesterol, was found out. A decrease in an oxidative stress has been established by reducing the level of malondialdehyde and increasing the activity of superoxide dismutase; there was also a reduction of the lipid accumulation in the liver and the prevention of morphological changes in the liver tissue in type 2 diabetes mellitus. The results obtained confirmed the traditionally declared benefits of *Zea maydis styli cum stigmatis* in diabetes mellitus and the antidiabetic potential of *Zea maydis styli cum stigmatis*, which can become the basis for the development of affordable herbal remedies aimed at the treatment of type 2 diabetes [38].

An *in vivo* study of the *Zea maydis styli cum stigmatis* effect on glycemic metabolism in the laboratory mice with experimental diabetes induced by alloxan and adrenaline, was carried out. It was found out that after the oral administration of the *Zea maydis styli cum stigmatis* extract to mice, the level of glucose and glycosylated hemoglobin in the blood significantly decreased, while the level of insulin secretion was markedly increased. At the same time, against the background of taking the *Zea maydis styli cum stigmatis* extract, a gradual restoration of pancreatic beta cells was observed, and the body weight of the animals also increased [39].

The researchers who had studied the antidiabetic, antioxidant, and antihyperlipidemic activities of the fraction of phenolic compounds isolated from *Zea maydis styli cum stigmatis* in the experiments *in vivo*, came to a similar conclusion. The authors showed that the use of this fraction significantly reduced weight loss, water consumption and especially the concentration of glucose in the blood of mice with experimental diabetes, which indicated its potential antidiabetic activity. Alongside with this, there was a decrease in the level of malondialdehyde, total cholesterol, triacylglycerol, low density lipoproteins, and the amount of high density lipoproteins increased [40].

Pan Y. et al. focused their attention on the study of the antidiabetic effects of the polysaccharide obtained from *Zea maydis styli cum stigmatis*. *In vivo,* on the model of experimental diabetes in mice, it was found out that the use of a polysaccharide led to the stabilization of the animals' body weight, a decrease in blood glucose and serum insulin levels, and an improvement in glucose tolerance. There was a decrease in the level of glycated

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Scientific and Practical Journal
PHARMACY & PHARMACOLOGY

whey protein and non-esterified fatty acids, as well as a marked increase in the activity of superoxide dismutase, glutathione peroxidase and catalase. In addition, the isolated polysaccharide also showed a cytoprotective effect in histopathological observations [41].

The evaluation results of the inhibitory effect of *Zea maydis styli cum stigmatis* polysaccharides on α-glucosidase and α-amylase *in vivo* are presented. It has been shown that *Zea maydis styli cum stigmatis* polysaccharides can significantly inhibit these enzymes and increase glucose uptake by skeletal muscle cells, which allows us to consider them potentially useful for the treatment of type 2 diabetes mellitus [42].

An *in vitro* model was used to establish the inhibitory effect of the *Zea maydis styli cum stigmatis* extract on the formation of carboxymethyllysine, which is the end product of glycation and is currently considered a biological marker of diabetes. It was found out that the inhibition degree in the formation of carboxymethyllysine by the *Zea maydis styli cum stigmatis* extract was 76.57%. The authors of the studies showed that the *Zea maydis styli cum stigmatis* extract suppressed the formation of carboxymethyllysine due to the absorption of glyoxal/methylglyoxal or due to its antioxidant activity associated with the content of flavonoids in it [43].

Alongside with maisin, an antidiabetic activity is highly likely to be characteristic of *Zea maydis styli cum stigmatis* apigenin and luteolin derivatives. The antioxidant activity of the ethyl acetate fraction of *Zea maydis styli cum stigmatis* and its ability to inhibit α-amylase and α-glucosidase in enzymatic reactions were studied in the *in vitro* experiments. The results of the studies confirmed the presence of a pronounced antioxidant effect of *Zea maydis styli cum stigmatis*, which may be required for the prevention and treatment of diabetes mellitus and its complications, including diabetic nephropathy [44].

The results of the *in vivo* studies devoted to the research of the mechanism reducing the glucose level in the blood of mice under the influence of *Zea maydis styli cum stigmatis,* have been published. The ability of saccharides and phenolic compounds of *Zea maydis styli cum stigmatis* to inhibit intestinal α-glucosidases was evaluated in the work. Synthetic drugs from the group of α-glucosidase inhibitors have a number of gastrointestinal side effects and not all of them are commercially available. The results of the study showed that the polyphenolic compounds of *Zea maydis styli cum stigmatis* had an effective inhibitory action on intestinal α-glucosidases. An *"in silico"* analysis of the *Zea maydis styli cum stigmatis* polyphenols showed that maisin can be responsible for the inhibition of α-glucosidases [45].

The leading protective role against damage to endothelial cells of the vascular tissue under the conditions of high glucose levels is assigned to the polyphenolic compounds of *Zea maydis styli cum stigmatis*. The protective effect was studied *in vitro* using human umbilical vein endothelial cells, and subsequently *in vivo* in the rats with streptozocin-induced diabetes. It has been shown that the phenolic fraction of *Zea maydis styli cum stigmatis* can have a positive effect on patients with diabetes and play a significant role in preventing the development and progression of diabetic complications such as diabetic nephropathy and atherosclerosis [46].

### 2.2.4. Weight loss, lipid-lowering effect

Alongside with the anti-diabetic effect of *Zea maydis styli cum stigmatis* shown in various studies, there are reports of their ability to reduce body weight. One of such *in vivo* studies showed that the oral administration of the *Zea maydis styli cum stigmatis* extract high in maisin to mice, resulted in the inhibition of the expression of the genes involved in adipocyte differentiation, reduced fat accumulation and synthesis, and promoted the expression of the genes involved in lipolysis and fat oxidation [47].

The results of the *Zea maydis styli cum stigmatis* extract effect on cholesterol metabolism in the *in vivo* experimental model in mice on a high-fat diet have been published. It has been found that the addition of the *Zea maydis styli cum stigmatis* extract alongside with the diet enriched with fats, improves the level of adipocytokines secretion and glucose homeostasis. Alongside with this, the *Zea maydis styli cum stigmatis* extract has been shown to be effective in lowering the cholesterol pool in the liver, consistent with lowering blood and liver cholesterol levels [48].

In the review study, Wang B. et al. emphasized that the lipid-lowering properties of *Zea maydis styli cum stigmatis* are extremely relevant for the prevention and treatment of the metabolic syndrome, including obesity, hypertension, hyperglycemia, and abnormal levels of triglycerides and high-density lipoprotein cholesterol [49].

An *in vivo* study of the potential anti-obesity activity of maisin was carried out by Lee C. et al. in several groups of mice that received food with different fat contents. In the animals, body weight and body fat were measured, as well as mRNA expression levels of proteins involved in adipocyte differentiation, fat accumulation, fat synthesis, lipolysis, and fat oxidation in the adipose tissue and liver. It was found out that maisin reduced the level of intracellular lipid droplets and triglycerides, and suppressed lipid accumulation and adipocyte differentiation. In addition, maisin has been shown to cause apoptotic death of preadipocytes, which may ultimately lead to a decrease in adipose tissue mass. Alongside with this, weight gain and fat mass in the mice decreased, the levels of thyroglobulin, total cholesterol, low-density cholesterol and glucose in blood serum decreased. On the whole, the effects obtained made it possible to suggest that maisin had anti-obesity effects *in vivo,* and this compound could be used as a functional food ingredient or as a drug for the prevention and treatment of obesity [50].

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Similar results were found out when studying the effect of the *Zea maydis styli cum stigmatis* extract and phytosterol on adipocyte growth factors. The oral administration of the subjects under *in vivo* study showed a significant reduction in weight and a decrease in the number of adipocytes in the liver and adipose tissue. The combined use of the *Zea maydis styli cum stigmatis* extract and phytosterol has demonstrated the ability to effectively reduce preadipocyte differentiation by inhibiting the activity of adipocyte growth factors [51].

The effect of the *Zea maydis styli cum stigmatis* decoction on the lipid profile was studied *in vivo* in patients with angina pectoris. A meta-analysis of several randomized trials has been published, indicating that the use of the *Zea maydis styli cum stigmatis* decoction contributed to the normalization of high-density lipoprotein levels and the reduction of total cholesterol and low-density lipoprotein in patients with angina pectoris. The authors suggested that the *Zea maydis styli cum stigmatis* decoction alone, as well as in the combination with a traditional drug treatment, might have a beneficial effect on blood lipids [52].

### 2.2.5. Antitumor activity

The recent studies devoted to the research of the possible *Zea maydis styli cum stigmatis* antitumor activity are of undoubtful interest.

The results of *in vivo* studying the *Zea maydis styli cum stigmatis* effect on tumor growth and immunological parameters in mice with experimental hepatocarcinoma, have been published. The study demonstrated that *Zea maydis styli cum stigmatis* could not only suppress tumor growth, but also increase the survival time of mice. In addition, the introduction of *Zea maydis styli cum stigmatis* contributed to an increase in body weight, a number of peripheral leukocytes, and a number of other indicators of the immune system functioning [53].

The data that give evidence of the significant effectiveness of the *Zea maydis styli cum stigmatis* extracts for the treatment of benignant and malignant prostate gland diseases have been presented. In particular, a study has been conducted to investigate the effect of the *Zea maydis styli cum stigmatis* extract on benignant prostatic hyperplasia. The experiments were carried out *in vivo* on male rats divided into groups receiving hormone therapy with testosterone, and combination therapy with testosterone and the *Zea maydis styli cum stigmatis* extract. It was found out that this treatment with the *Zea maydis styli cum stigmatis* extract led to a noticeable decrease in the weight of the prostate gland and alleviated the symptoms of the disease [54].

The *in vitro* study results of the antioxidant and antitumor activities of the *Zea maydis styli cum stigmatis* phenolic compounds of different corn varieties in relation to breast carcinoma cells have been obtained. The results of the study showed a correlation between the total content of phenolic compounds, the antioxidant activity and cytotoxicity against breast carcinoma cells [55].

The antitumor properties of the *Zea maydis styli cum stigmatis* extract have been investigated in relation to human breast cancer. The cytotoxicity of the extract was evaluated *in vitro* on MCF-7 breast cancer cells in comparison with normal human mesenchymal cells. The results of the studies led to the conclusion that the *Zea maydis styli cum stigmatis* extract reduced the viability of malignant cells and increased their apoptosis in a dose-dependent manner [56].

A potential antitumor activity of maisin isolated from the *Zea maydis styli cum stigmatis,* was evaluated *in vitro* on androgen-independent human prostate cancer cells. It turned out that maisin dose-dependently reduced the viability of cancer cells and significantly induced their apoptotic death. It has been shown that the combined treatment with maisin and other antitumor agents synergistically enhances the death of malignant cells. These results show for the first time that maisin can have a pronounced therapeutic potential for the treatment of chemoresistant or androgen-independent human prostate cancer [57].

The ability to significantly inhibit the proliferation of pancreatic cancer cells *in vitro* and *in vivo* has been established for the crude *Zea maydis styli cum stigmatis* polysaccharide. The studies have shown that this polysaccharide can induce apoptosis of pancreatic cancer cells, stop the cell cycle, and prevent migration and invasion of pancreatic cancer cells [58].

### 2.2.6. Immunotropic action

Attention is drawn to the studies' results of the *Zea maydis styli cum stigmatis* effect on immunity parameters. Scientists of the Korean Immunological Center Kim K.A., Choi S.K., Choi H.S. found out *in vitro* that the *Zea maydis styli cum stigmatis* extracts alter the activity of mouse macrophages, stimulating the production of cyclooxygenase and oxidase synthase. The involvement of *Zea maydis styli cum stigmatis* components in immunological reactions has also been reported previously, in particular, their ability to suppress a tumor necrosis factor and adhesion of bacterial lipopolysaccharides on cell walls [59, 60].

It has been supposed that the immunological properties of *Zea maydis styli cum stigmatis*, as well as some other types of activity of this raw material, may be due to the presence of maisin. In particular, the ability of maisin to activate macrophages was evaluated *in vitro* using mouse cells. It has been found out that maisin dose-dependently increased the secretion of a tumor necrosis factor and the production of nitric oxide synthase by 11.2 and 4.2 times, respectively, compared with untreated control cells. These results make it possible to prognose that maisin can be a new immunomodulator that enhances an early innate immunity [61].

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Scientific and Practical Journal
PHARMACY & PHARMACOLOGY

### 2.2.7. Anti-inflammatory action

*Zea maydis styli cum stigmatis* attracted scientists' attention in terms of studying their possible anti-inflammatory action. Experimental carrageenan-induced pleurisy in rats was used as a model for studying this type of activity *in vivo*. It was found out that pretreatment with the *Zea maydis styli cum stigmatis* extract reduced the volume of exudate, the number of leukocytes in the focus of inflammation, the level of an oxidative stress, and the values of other markers of the inflammatory process [62].

For the treatment of the oral cavity diseases, the drug "Insadol", which included the *Zea maydis styli cum stigmatis* extract, was previously used. "Insadol" was registered as an anti-inflammatory drug with the ability to stimulate mucosal repair, reduce pain, reduce gums bleeding and was previously used to treat the oral cavity diseases [63].

### 2.2.8. Antioxidant action

Various groups of scientists have suggested a possible relationship between the established types of the *Zea maydis styli cum stigmatis* activity and the antioxidant properties of this MPRM. The work by Maksimovic Z.A. and Kovacevic N. is devoted to a focused study of the antioxidant effect of *Zea maydis styli cum stigmatis*. The scientists obtained a methanol *Zea maydis styli cum stigmatis* extract and fractionated it using mixtures of different polarity solvents. The isolated fractions were studied for the presence of the antioxidant activity *in vitro* using the TBARS test, which makes it possible to assess the degree of lipid peroxidation. The maximum activity was found out in lipophilic fractions, the components of which were phenolic acids, flavonoid aglycones (flavones, flavonols, and methylated flavones), as well as flavonoid monosides [64].

The antioxidant properties of the *Zea maydis styli cum stigmatis* extract made it possible to consider it as a potential remedy for the treatment of toxic hepatitis. On the model of experimental acute toxic hepatitis induced in laboratory rats by the exposure to the trichloromethane solution, it was found out that the dry extract of *Zea maydis styli cum stigmatis* demonstrates hepatoprotective properties and is a low-hazard substance. It has been shown *in vitro* that the mechanism of the studied extract's action is due to its antioxidant activity [28].

Antioxidant effects *in vivo* and *in vitro* are summarized and described in the work by Hasanudin K. et al., for heteropolar fractions obtained from *Zea maydis styli cum stigmatis.* Herewith, ethyl alcohol, methanol, dichloromethane and acetone were used. The same authors drew attention to the anti-inflammatory effect and a number of other *Zea maydis styli cum stigmatis* properties [2].

### 2.2.9. Antibacterial action

Quite recently, for the first time, the data were published regarding the evaluation of the antibacterial activity and the antibiotic-modulating action of the hexane extract of *Zea maydis styli cum stigmatis*. The studies have shown that the extract exhibited an antimicrobial activity against the strains of *Escherichia coli, Staphylococcus aureus,* and *Pseudomonas aeruginosa* [65].

### 2.2.10. Dermatoprotective action

*Zea maydis styli cum stigmatis* have good prospects to be used for suppressing skin pigmentation.

In particular, photoprotective effects of *Zea maydis styli cum stigmatis* have been studied *in vivo* by the oral administration of the aqueous extract of *Zea maydis styli cum stigmatis* to laboratory mice. The study showed that experimental therapy led to a decrease in the photoaging process, as evidenced by the positive dynamics of biological markers of this process. They are: a decrease in the thickness of the epidermis and the formation of wrinkles, a decrease in the expression of anti-inflammatory genes, a decrease in the level of lipid peroxidation of skin lipids and blood DNA, etc.). The authors suggested that these effects are achieved due to the content of compounds with a potential antioxidant and an anti-inflammatory activity in *Zea maydis styli cum stigmatis* [66].

The study of the *Zea maydis styli cum stigmatis* inhibitory effect on the production of melanin *in vitro* revealed that the *Zea maydis styli cum stigmatis* extract applied to the cells of pigmented melanocytes (melan-A) obtained from normal epidermal melanoblasts of C57BL inbred mouse embryos, reduced melanin production by 37.2% without any manifestation of cytotoxicity [67].

There is scientific evidence that also confirms the photoprotective properties of *Zea maydis styli cum stigmatis*. An *in vitro* study was conducted to research the prophylactic effect of the *Zea maydis styli cum stigmatis* extract on human keratinocytes. The cells were pretreated with the *Zea maydis styli cum stigmatis* extract and then exposed to ultraviolet. The results showed that the survival of keratinocytes after pre-treatment with the *Zea maydis styli cum stigmatis* extract was markedly increased. The *Zea maydis styli cum stigmatis* extract statistically significantly reduced intracellular damage caused by ultraviolet rays and slowed down the apoptosis reaction due to the stabilization of the mitochondrial membrane potential [68].

### 2.2.11. Neuroprotective action

The *in vitro* study results of the neuroprotective effect of maisin isolated from *Zea maydis styli cum stigmatis* are presented. The scientists found out that maisin pretreatment reduced the cytotoxic effect of hydrogen peroxide on neuroblastoma cells, weakened their apoptosis, and significantly and dose-dependently increased the levels of antioxidant enzymes. The obtained data suggested that maisin has a neuroprotective effect due to its antioxidant properties [69].

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Neuroprotective properties have also been studied for terpene compounds isolated from *Zea maydis styli cum stigmatis*. The studies were carried out *in vitro* on model human bone marrow neuroblastoma cells damaged by the exposure to hydrogen peroxide. The results showed that some of the studied substances inhibited apoptosis and had a statistically significant protective effect in relation to the experimental cell culture [70,71].

Thus, as a result of the conducted studies, it was revealed that at the present stage, scientific information on the pharmacological action of *Zea maydis styli cum stigmatis* has been significantly expanded. Generalized data on the main types of the *Zea maydis styli cum stigmatis* pharmacological action, established on the basis of information and analytical search, are presented in Table 2.

## CONCLUSION

Generalization and analysis of modern scientific literature data made it possible to establish that *Zea maydis styli cum stigmatis* are still in the sphere of scientists' interest, as evidenced by the information replenished and expanded in recent years, on their chemical composition and spectrum of pharmacological action. Alongside with the *Zea maydis styli cum stigmatis* flavonoids, other groups of PASs in this raw material are also actively studied. It was revealed that knowledge about potentially significant and confirmed types of *Zea maydis styli cum stigmatis* therapeutic actions has been significantly updated. In addition to the traditionally known choleretic, diuretic, hemostatic effects of *Zea maydis styli cum stigmatis*, their antioxidant, anti-inflammatory, antidiabetic, immunotropic, neuroprotective, antitumor, photoprotective and a number of other pharmacological effects significant for medicine, have been established. The results of this review may be useful for identifying promising directions for the development of drugs based on *Zea maydis styli cum stigmatis*.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## AUTHORS' CONTRIBUTION

Elena B. Nikiforova – determination of the aim and objectives of the study, information and analytical search on the topic of the study, writing the sections "Chemical composition of *Zea maydis styli cum stigmatis*", "Pharmacological properties of *Zea maydis styli cum stigmatis*"; Nafiset M. Bat – writing the sections "Introduction", "Conclusion"; Naira A. Davitavyan – preparation of references.

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