Journal of Medicinal and Chemical Sciences

Journal homepage: http://www.jmchemsci.com/

Original Article

Investigation of Allergenic and Mutagenic Effects of Phenolic Compound, an Arignase-2 Inhibitor

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ARTICLE INFO

Article history

Received: 2021-04-21
Received in revised: 2021-05-02
Accepted: 2021-05-20
Manuscript ID: JMCS-2104-1186
Checked for Plagiarism: **Yes**
Language Editor:
Dr. Behrouz Jamalvandi
Editor who approved publication:
Dr. Sami Sajjadifar

DOI:10.26655/JMCHEMSCI.2021.3.10

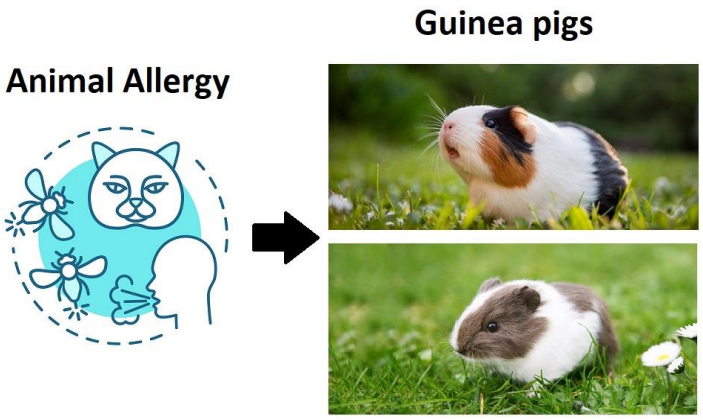
KEYWORDS

endothelial disfunction, arginase2, thrombin, arterial hypertension, allergenicity, mutagenicity, phenolic compound

ABSTRACT

A big risk factor for sensitization and allergic diseases is susceptibility to animal allergens. The most significant animal allergens are derived from mammals, besides mites and cockroaches. The experiments on the allergenic properties of KUD975 were carried out on bisexual sexually mature albino guinea pigs weighing 300 ± 20 g. During the initial assessment of allergenic and mutagenic properties, the allergenic properties of KUD975 were studied by setting up an active skin anaphylaxis reaction. Mutagenicity in the test of induction of dominant lethal mutations was studied. For research, outbred male rats weighing 180-220 g KUD975 was administered intragastrically at a dose of 106 mg/kg, which corresponds to a 40-fold estimated therapeutic dose. Planting intact females at the rate of 3 heads for each male was performed weekly according to the stages of spermatogenesis. The study of the allergenic effect in the formulation of the reaction of active skin anaphylaxis in guinea pigs and mutagenicity in the test for the induction of dominant lethal mutations of the phenolic compound methyl ester (2 - ((1-hydroxy naphthalene-2-yl) thio) acetyl) -D-proline under the laboratory code KUD975 showed no signs of allergenicity and mutagenicity of compound KUD975. Given the results of this study, as well as the previously conducted study of toxicological safety, pharmacological activity, methyl ester (2 - ((1-hydroxy naphthalene-2-yl) thio) acetyl) -D-proline KUD-975 can be recommended for further study as a medicinal agent acting on arignase-2 for the treatment and prevention of a number of endothelium-associated diseases.

GRAPHICAL ABSTRACT



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Introduction

Phenolic compounds are a class of secondary metabolites that play an important role in plants. Aside from their beneficial effects on the plant host, phenolic metabolites (polyphenols) have a number of biological properties that have a positive impact on human health. Plant phenolics, which can be obtained through the diet or through topical treatment, have been shown to relieve symptoms and prevent the development of various skin disorders. Phenolic compounds are a promising method in preventing the causes and effects of skin aging, skin diseases, and skin injury, including wounds and burns, due to their natural origin and low toxicity. Polyphenols often have a protective effect and can help avoid or slow down the development of some skin conditions, such as wrinkles and acne, as well as severe, potentially life-threatening diseases like cancer. The bovine mammary gland is a diverse and complex organ that consists of different types of cells that function together for milk synthesis and secretion purposes [1,2]. The blood-milk barrier that allows the exchange of solutes and macromolecules required for optimal milk production is formed by a layer of endothelial cells. However, during the bacterial challenge, endothelial cells redirect some of their lactation function by initiating inflammation to protect the underlying tissue from injury. Endothelial cells closely control the passage of plasma components and leukocytes into infected tissue at the start of inflammation [3]. The discovery of the active role of endothelium has led to significant progress in the study of the pathogenesis of cardiovascular diseases [4]. Typically, the term “endothelial function” or “endothelial function” refers to the ability of endotheliocytes to participate in the production of a wide range of vasoactive substances. Moreover, “endothelial dysfunction” (ED) is understood as a pathological condition, mainly characterized by an imbalance between substances with vasodilating, antimitogenic and anti-thrombogenic properties (endothelium-dependent relaxing factors) [5,6] and substances with vasoconstrictive, prothrombotic and proliferative dependent (endothelium-dependent narrowing factors) [7]. In clinical practice, ED is associated primarily with various violations of the conditions of capillary blood flow, which provides the required cellular metabolism. It is important to note that the vast majority of cardiovascular risk factors are associated with ED [8–10].

The cytotoxic, genotoxic, apoptotic, and receptive oxygen species (ROS)-producing impacts of carvacrol on gastric adenocarcinoma in vitro were investigated. For these reasons, human gastric adenocarcinoma (AGS) cells were utilized and broke down after 24 h of introduction to carvacrol with various fixations. The cytotoxicity, ROS age, glutathione (GSH) level, and genotoxicity were researched by the ATP cell feasibility measure, 2′,7′-dichlorodihydrofluorescein-diacetate test, GSH/GSSG-Glo examine, and comet test, individually. Apoptosis acceptance was identified by acridine orange/ethidium bromide recoloring and western smudging underneath the half-maximal development inhibitory fixation esteem. Carvacrol demonstrated cytotoxic, genotoxic, apoptotic, ROS producing, and GSH-diminishing impacts on AGS cells in a portion subordinate way [11–13]. There was a nearby negative connection between cell practicality and ROS level. Carvacrol restrained the multiplication of AGS cells, recommending that it may be a novel and solid anticancer specialist against the human gastric adenocarcinoma. These outcomes uphold the interest of regular eating routine parts in the advancement of restorative items for infections [14].

There is sound reasoning for considering polyphenolics as significant supporters of the dietary anti-oxidant consumption got from leafy foods [15]. In any case, proceeding with research is required utilizing suitable biomarkers of oxidant harm in vivo before these mixes can be decisively considered as dietary anti-oxidants with healthful advantage [16].

It has been recommended that the gathering of flavonoids could be a critical advance being

developed of plant resilience to various natural anxieties. Besides, it has been perceived that abiotic stresses, for example, dry season and UV-B radiation (280–315 nm), actuate phenolic compound collection, propose a part for these mixes in dry spell resilience. The impact of UV-B introduction on stew pepper (Capsicum annuum, cv. 'Coronel') plant execution, phenolic compound creation, and quality articulation related to the reaction to resulting dry spell pressure were assessed. Moreover, the phenotypic reaction to dry season pressure of these plants was considered [17].

An essential data about the antioxidative action and phenolic aggravates profiles in natural products, leaves, and foundations of Korean ginseng with development years were given. This data is conceivably helpful to ginseng cultivators and ventures engaged with the creation of high-caliber and wholesome ginseng items [18].

Despite significant progress in the study of methods of pharmacological correction of endothelial dysfunction, currently, there are no drugs - edothelioprotectors. Given this fact, the problem of developing and studying innovative drugs, the main mechanism of action of which is associated with targets of the pathogenetic cascade L-arginine-eNOS–NO, is an urgent problem in modern pharmacology and medicine [19,20].

In the framework of this preclinical study of the toxicological safety of the developed phenolic compound, an arginase-2 inhibitor, with the laboratory code KUD-975 (methyl ether (2 - ((1-hydroxy naphthalene-2-yl) thio) acetyl) -D-proline), we carried out short-term screening study of its allergenicity and mutagenicity.

In short-term screening tests, we evaluated the allergenic effect and mutagenicity of the drug candidate test - methyl ester (2 - ((1-hydroxy naphthalene-2-yl) thio) acetyl) -D-proline (laboratory code KUD975).

Material and methods

The experimental study was conducted at the Research Institute of Pharmacology of Living Systems of Belgorod State National Research University. The study was performed in compliance with the requirements of General Requirements for the Competence of Testing and Calibration Laboratories 17025-2009, GOST R ISO 5725-2002, and the Rules of Laboratory Practice, approved by order of the Ministry of Healthcare and Social Development of the Russian Federation dated August 23rd, 2010 № 708n.

Allergenicity

The experiments on the allergenic properties of KUD975 were carried out on bisexual sexually mature albino guinea pigs weighing 300 ± 20 g. KUD975 was administered intragastrically in the form of a suspension in 1% starch paste using a specially made atraumatic probe based on 0.1 ml of suspension per 10 g of animal body weight [21–23]. As a control, we used data obtained in animals with intragastric administration of an appropriate placebo volume of 1% starch paste. The double daily therapeutic dose of the studied drug for guinea pigs was 5.3 mg/kg/day, eight times - 21.2 mg/kg/day.

During the initial assessment of allergenicity and mutagenicity, the study of the allergenic properties of KUD975 was carried out by setting the reaction of active skin anaphylaxis.

Animals were divided into the following groups (10 in a group, five females and five males): I - control; II - KUD975 at a dose of 5.3 mg/kg/day.; III - KUD975 at a dose of 21.2 mg/kg/day.

The sensitization of guinea pigs with the studied drug was done by intragastric administration within 30 days. The day after the last injection, anaphylactogenic activity in the reaction of active skin anaphylaxis was assessed by intradermal (in the back) administration of a resolving dose of the studied drug in a volume of 0.05 ml, and to control skin reactivity, 0.05 ml of a sterile isotonic solution was injected into another skin area sodium chloride.

The resolving dose was selected experimentally so as not to cause irritation at the injection site. To determine the resolving dose, five males and

five females of albino guinea pigs were used. 0.05 ml of an aqueous solution of KUD975, tablets coated with a film coating, 10 mg in the following concentrations: 20%, 10%, 5%, 2%, 1% were injected intradermally at each point in each guinea pig at various points in the back. Then, the injection sites were monitored for three hours in order to determine the possible local irritant effect. It was found that after intradermal administration of 20% and 10% solutions of KUD975, tablets, film-coated tablets, 10 mg, signs of local irritation were observed, consisting of local reddening of the skin. Intradermal administration of 5%, 2%, and 1% aqueous solutions of KUD975, tablets, film-coated tablets, 10 mg in the indicated volume did not lead to the appearance of signs of locally irritating effect. Thus, in further experiments, the maximum concentration of the compound, which did not have a locally irritating effect upon intradermal administration, was used — 5%. After 20-25 minutes, animals were injected intravenously with 0.5 ml of 1% Evans blue solution. 30 minutes after this, the animals were euthanized, and the size of the blue spot on the inside of the skin at the injection site was determined using a caliper.

The study of mutagenicity in the test of induction of dominant lethal mutations

For the research, outbred male rats weighing 180-220 g KUD975 was administered intragastrically at a dose of 106 mg/kg, which corresponds to a 40-fold estimated therapeutic dose. Planting intact females at the rate of 3 heads for each male was performed weekly according to the stages of spermatogenesis: The 1st week after the administration of the preparation - mature spermatozoa, the 2nd week - late spermatids, the 3rd week - early spermatids, the 4th week - late spermatocytes 5th week - early spermatocytes. With such a formulation of the experiment, the possible different sensitivity of male germ cells during the period of premiotic, meiotic, and postmeiotic stages was taken into account.

Pregnant females were decapitated on the 18-20th days of pregnancy. The number of yellow bodies of pregnancy, implantation sites, and the number of resorbed, dead, and living embryos was counted. By the ratio of relevant indicators, pre-, post-implantation, and total embryonic mortality were determined, and the average number of implantation sites and live embryos per female was calculated.

The fertility of males was determined by the ratio of the number of transplanted females to the number of fertilized (%).

The results were statistically processed by calculating the arithmetic mean (M) and standard error of the mean (± m). Assessment of the statistical significance of differences in intergroup comparisons was carried out according to the bilateral Student t-test for independent groups. Differences were considered statistically significant at p values $p<0.05$.

Result and Dissection

During the study of the allergenic properties of KUD975 while the formulation of the reaction of active skin anaphylaxis, it was found that the studied drug in two and eight times daily therapeutic dosages did not have allergenic properties (Table 1).

Table 1: The results of the study of the allergenic properties of the drug KUD975 in the formulation of the reaction of active skin anaphylaxis

Group	Drug / Dose / Injectable	Spot size, mm
I	Control (placebo), the dose of the drug	3.17±0.1
	Control (placebo), reactivity control	3.02±0.1
II	KUD975 5.3 mg/kg, resolving dose of the drug	3.14±0.1
	KUD975 5.3 mg/kg, reactivity control	3.03±0.1
III	KUD975 21.2 mg/kg, resolving dose of the drug	3.11±0.1
	KUD975 21.2 mg/kg, reactivity control	3.19±0.1

We found that in guinea pigs sensitized by the studied preparation, the sizes of exudate spots formed at the points of introduction of permissive doses reached a diameter of 3.5 mm and, on average, did not statistically significantly exceed the sizes of exudate spots at control points and control animals.

Thus, in the reaction of active skin anaphylaxis in guinea pigs, the allergenic properties of the drug KUD975 in two and eight times daily therapeutic doses were not detected.

The results of the evaluation of the mutagenic activity of KUD975, film-coated tablets, 10 mg in the induction test of dominant lethal mutations are presented in table 2.

With the administration of KUD975 tablets, 10 mg at a dose of 106 mg/kg, male fertility at all stages of spermatogenesis did not differ from the control values. The number of implantation sites, live embryos, pre-, post-implantation, and total embryonic death of embryos for all stages of spermatogenesis were also within the control values (Table 2).

The study did not establish an increased sensitivity of male sex cells to the effects of KUD975 at any individual stages of spermatogenesis.

Table 2: Assessment of KUD975 mutagenicity in the test of induction of dominant lethal mutations in rats with intragastric administration at a dose of 106 mg/kg

Spermatogenesis stages	Experimental series	Male fertility, %	Number of implantation sites per female (M ± m)	Number of live embryos per female (M ± m)	Preimplantation death, % (M± m)	Post-implantation death, % (M± m)	Total embryonic death, %
Mature sperm	Treated	81.8	10.1±1.9	8.4±0.2	5.67±3.45	7.66±2.13	11.3±2.9
	Control	85.3	9.4±0.2	8.0±0.8	4.72±2.04	8.39±2.06	9.8±2.1
Late spermatids	Treated	76.1	10.2±0.9	8.1±1.7	6.81±3.27	7.41±2.21	10.1±3.2
	Control	83.1	9.9±0.7	8.6±1.2	7.90±1.76	5.39±0.19	11.9±3.9
Early spermatids	Treated	79.5	10.4±2.1	8.2±1.2	6.04±2.48	8.40±1.54	10.1±6.3
	Control	79.1	9.7±1.0	9.0±0.7	3.87±2.32	9.18±3.61	9.64±1.9
Late spermatocytes	Treated	83.2	10.8±0.3	8.0±0.9	4.93±4.11	10.82±1.13	7.59±2.6
	Control	81.9	10.3±1.0	8.9±1.1	6.38±2.70	9.66±4.32	8.5±2.9
Early spermatocytes	Treated	80.2	8.9±0.7	8.1±0.8	3.97±4.17	5.79±2.27	10.7±3.1
	Control	82.3	9.0±0.4	7.4±1.0	3.82±1.74	6.61±1.93	9.4±2.7

Note: * - $p < 0.05$ - in comparison with the control group

Thus, KUD975, when administered intragastrically to male rats at a dose of 106 mg/kg, did not exhibit mutagenic activity on germ cells of male rats in the experimental groups.

The results of the work of scientists today have led to the understanding of the fact that the preservation of the vascular endothelium is fundamental to maintaining the normal functioning of the cardiovascular system, as well as in the prevention and treatment of a wide range of endothelium associated pathology [24–26].

The development of new arginase inhibitors is a promising strategy for the treatment of diseases caused by disorders associated with the production and functioning of NO. The number of potential indications for the use of arginase inhibitors is wide and includes cardiovascular,

pulmonary, metabolic, and neurological problems [27].

We believe that an important role in the implementation of the pathogenesis of a wide range of endothelium-associated pathology of arginase-2 requires an increased concentration of forces of scientists of medicinal chemists and pharmacologists in the development of drugs that selectively inhibit this enzyme.

Previously, we developed and studied acute toxic effects [28,29] and the pharmacological activity of a number of phenolic compounds that are inhibitors of arginase-2 and thrombin. The pharmacological activity of the developed compounds is shown in our laboratory on various experimental models of endothelial dysfunction [30,31]. The leader – methyl ether (2 - ((1-hydroxy-naphthalen-2-yl) thio) acetyl) -D-proline compound was selected under the laboratory code KUD-975.

Studies of the toxicological safety of innovative drugs are an essential link that can limit the further clinical study and use of the developed substances, the effectiveness of which has been proven in experimental models and in vitro. An integral part of toxicological safety studies is the study of specific types of toxicity.

Conclusion

The study of the allergenic effect in the formulation of the reaction of active skin anaphylaxis in guinea pigs and mutagenicity in the test for the induction of dominant lethal mutations of the phenolic compound methyl ester (2 - ((1-hydroxy naphthalene-2-yl) thio) acetyl) -D-proline under the laboratory code CUD -975 showed no signs of allergenicity and mutagenicity of compound KUD975. Given the results of this study, as well as the previously conducted study of toxicological safety, pharmacological activity of methyl ester (2 - ((1-hydroxy naphthalene-2-yl) thio) acetyl) -D-proline can be recommended for further study as a drug acting on arignase-2 for the treatment and prevention of endothelium-associated diseases.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

All authors contributed toward data analysis, drafting and revising the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

We have no conflicts of interest to disclose.

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HOW TO CITE THIS ARTICLE
Liliya V. Korokina , Mikhail V. Pokrovskii, Indira S. Kochkarova, Olga N. Pokopeiko, Sergey V. Povetkin. Investigation of Allergenic and Mutagenic Effects of Phenolic Compound, an Arignase-2 Inhibitor, *J. Med. Chem. Sci.*, 2021, 4(3) 301-307
DOI: 10.26655/JMCHEMSCI.2021.3.10
URL: http://www.jmchemsci.com/article_130832.html