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ANTIBACTERIAL PROPERTIES OF *Ginkgo biloba* EXTRACT ON MICROORGANISM STRAINS *IN VITRO* EXPERIMENTS

Tetiana FOTINA[1], Roman PETROV[1], Hanna FOTINA[1, 3], Oksana SHKROMADA[1], Roman YAROSHCHUK[1], Anatoliy FOTIN[1], Volodymyr ZAZHARSKY[2], Oleksiy FOTIN[1], Hryhoriy HAVRYLIUK[1], Svitlana YAROSHCHUK[1]

[1]Sumy National Agrarian University, 160, G. Kondratieva, Sumy, 40021, Ukraine
[2]Dnipro State Agrarian and Economic University, 25, Voroshylova Str., Dnipro, 49027, Ukraine
[3]Institute of Parasitology, Biology Centre of the Czech Academy of Sciences, Branišovská 1160/31, 370 05 České Budějovice 5, Czech Republic

Corresponding author email: jaroschukr@ukr.net

Abstract

The pressing issue of antibiotic resistance demands immediate attention. Scientists are exploring alternative remedies, including plant-based solutions, to prevent infectious diseases. This study investigates the antibacterial properties of Ginkgo biloba extract in vitro. Ginkgo biloba contains specific compounds - terpenlactones (terpenic lactones: ginkgolides, bilobalides) and flavonoglycosides (flavonoids: quercetin, kaempferol, isorhamnetin, proanthocyanidins), which regulate metabolic processes, normalize cellular metabolism, and improve blood rheology and microcirculation. The research aims to examine the antimicrobial effects of ethanolic Ginkgo biloba extract on various strains of microorganisms in experiments conducted in vitro. The antibacterial activity of the plant extract was evaluated using the disc diffusion method against reference strains of Enterobacteriaceae, Pseudomonadaceae, Staphylococcaceae, Bacillaceae, Listeriaceae, Campylobacter jejuni, Corynebacterium xerosis, and Candida albicans. The experiments demonstrated significant antibacterial efficacy against a range of microorganisms, suggesting the potential of Ginkgo biloba extracts in combating polyresistant strains. This research received support from the Ministry of Education and Science of Ukraine (grant 0117U006533).

Key words: *antibacterial properties, disc diffusion method, Ginkgo biloba, reference strains.*

INTRODUCTION

Antimicrobial resistance poses a health risk to citizens that is escalating and has a global impact. Governments worldwide are increasingly focusing attention on this issue, as it threatens both modern human and veterinary medicine (Salmanov, 2016). The post-antibiotic era, where common infections and minor injuries can prove fatal, is far from an apocalyptic fantasy; it is a potential reality for the twenty-first century. This situation is exacerbated by the fact that antimicrobial agents have become an integral part of modern medicine and are widely used in veterinary practice (Lazăr et al., 2018).

The number of bacteria resistant to antibiotics transmitted from animals to humans is increasing daily, as essentially the same antibiotics used for human treatment are also used for animals. In human medicine, antibiotics are used only when necessary, unlike in veterinary medicine (Aarestrup, 2005; Aarestrup et al., 2008). Through specific mutations, bacteria become resistant or insensitive to many antimicrobial agents. Their excessive use in animal husbandry is one reason why key drugs are ineffective or marginally effective in human treatment. The greatest danger posed by the development of antimicrobial resistance in veterinary medicine is the biotransformation of antibiotics from animal products into the human body (Bacanlı & Başaran, 2019). The widespread use of antibiotics in animal husbandry leads to bacteria mutating and adapting, rendering antibiotics ineffective against them. Resistant bacteria are transmitted from animals to humans. In this regard, there are many antibiotics used in veterinary medicine that are more problematic than salinomycin, as it is exclusively applied in animal husbandry. What's even worse is that animals are often given the same antibiotics as humans. In the event of a person becoming infected from a live animal or through its raw meat with resistant

bacteria, treating the disease with the antibiotic previously administered to the animal becomes impossible (Carvalho & Santos, 2016; Cassini et al., 2019). According to EU estimates, 25,000 deaths per year are attributed to resistant bacteria. Currently, approximately 700,000 people die annually from diseases caused by resistant bacteria. According to projections by the World Health Organization, by 2050, antibiotics will cause the deaths of 10 million people per year – more than the current deaths from oncological diseases – and annual losses to the global economy will exceed 100 trillion USD. According to the Food and Agriculture Organization of the United Nations (FAO), antimicrobial resistance contributes to the increase in the price of animal products and reduces their quality (Liu et al., 2022; 2023; Desmoulin et al., 2024).

Today, antimicrobial resistance of microorganisms, according to the World Health Organization (WHO), is one of the most serious threats to human health. Bacterial resistance to antibiotics (AMR) increases every year. This is due to the excessive and uncontrolled use of antibiotics in medicine, veterinary medicine, agriculture, as well as their presence in soil and water. According to the US Expert Panel on Antibiotic-Resistant Bacteria, approximately 73 billion single doses or 300,000 tons of antibiotics are used annually worldwide (Bhardwaj et al., 2022; Xu et al., 2023).

The situation is further complicated by the fact that antimicrobial agents have become an integral part of modern human medicine and are widely used in veterinary practice. The number of different resistant (antibiotic-resistant) bacteria transmitted from animals to humans increases daily, as essentially the same antibiotics used for human treatment are also used for animals. Unlike animals, antibiotics are used in humans only when needed. Through specific mutations, bacteria become resistant or insensitive to many antimicrobial agents. Their excessive use in animal husbandry is one of the reasons why key drugs are ineffective or marginally effective in human treatment (Shkromada et al., 2022; 2024).

The most significant danger posed by the development of antimicrobial resistance in veterinary medicine is the biotransformation of antibiotics from animal products into the human body (Furtula et al., 2010; Aguidissou et al., 2019). According to EU estimates, 25,000 deaths per year are directly linked to resistant bacteria. Currently, approximately 700,000 people die annually from diseases caused by resistant bacteria. According to the Food and Agriculture Organization of the United Nations (FAO), antimicrobial resistance contributes to the increase in the price of animal products and reduces their quality (Food Safety, 2020; OECD/FAO, 2020). Antibiotic resistance in *Enterococus faecalis*, *Proteus vulgaris*, *Serratia marcescens*, *Yersinia enterocolitica*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Campylobacter jejuni*, *Staphylococcus epidermidis*, *S. aureus*, *Bacillus subtilis*, *Listeria innocua*, *L. monocytogenes* complicates infectious disease prevention measures and reduces the therapeutic effectiveness of antibacterial drugs (Sajid et al., 2016; Zhu et al., 2022). Therefore, the development of alternative methods for preventing animal diseases is relevant.

Currently, the use of plant extracts as an alternative to antibacterial drugs, including *Ginkgo biloba* extract, is relevant. *Ginkgo biloba*, also known as maidenhair tree or katsura tree, has been used in traditional Eastern medicine for centuries. It belongs to the *Ginkgoaceae* family, and its leaves, seeds, and fruits are used as medicinal raw materials (Mdzinarishvili et al., 2012; Kulić et al., 2022; Liu et al., 2022).

Considerable clinical experience has been accumulated regarding *Ginkgo biloba*, confirming its effectiveness in treating cerebral insufficiency, neurosensory disorders, and peripheral vascular diseases (Kuznetsova et al., 2016; Savaskan et al., 2018).

Ginkgo biloba contains specific compounds such as terpene lactones (ginkgolides, bilobalides) and flavonoglycosides (flavonoids: quercetin, kaempferol, isorhamnetin, proanthocyanidins), which affect metabolic processes, normalize cellular metabolism, and improve blood rheology and microcirculation (Herrschaft et al., 2012).

Preparations and dietary supplements based on *Ginkgo biloba*: stimulate the biosynthesis of endothelial relaxing factor and prostacyclin in the vascular wall; exert inhibitory effects on

platelet activation factor; increase the elasticity and strength of blood vessel walls (angioprotective action); hinder the aggregation of erythrocytes and platelets, prevent thrombosis, including in cerebral and coronary vessels (anti-aggregant, antithrombotic action); promote the dilation of small arteries and increase venous tone, improve capillary blood flow in organs and tissues; enhance cerebral blood flow and supply the brain with oxygen and glucose; alleviate circulatory insufficiency of atherosclerotic origin; increase neuronal survival under hypoxic conditions (vasoregulatory, venotonic, antihypoxic action); contribute to reducing the permeability of the vascular wall, both in the brain and peripherally; inhibit the development of traumatic or toxic brain edema (antiedematous action); hinder the formation of free radicals and lipid peroxidation in cell membranes, stabilize cell membranes (antioxidant action); normalize mediator processes in the central nervous system (CNS), affect the release, reuptake, and catabolism of neurotransmitters and their binding to neuronal membrane receptors; stimulate the release and inhibit the reuptake of norepinephrine and dopamine (antidepressant action); increase the sensitivity of postsynaptic muscarinic receptors to acetylcholine (nootropic action); contribute to improving cognitive functions in cerebral insufficiency: restore memory, ability to concentrate, language and motor functions of the CNS; provide a positive effect in disorders of peripheral circulation: obliterative atherosclerosis of the lower limbs, diabetic microangiopathy, hearing and vision impairments (retinopathy) due to aging, erectile dysfunction of vascular origin, and other conditions accompanied by chronic ischemia of peripheral tissues or organs.

When taken orally, *Ginkgo biloba* extract is well absorbed from the gastrointestinal tract.

The maximum concentration in plasma is reached within 1-2 hours. The half-life period is 4-5 hours. Determination of toxicity parameters is a mandatory step in preclinical studies of promising drug compounds.

The expression of reactive nitrogen intermediates from the catalytic action of inducible nitric oxide synthase (NO) in response to cytokines or molecules obtained from pathogens is of great importance for the control and destruction of intracellular microorganisms such as *Toxoplasma gondii*, *Leishmania major*, *Listeria monocytogenes*, *Mycobacterium leprae* and *Mycobacterium tuberculosis*.

The aim of the research was to study the antimicrobial properties of the ethanol extract of *Ginkgo biloba* on strains of microorganisms from the families *Enterobacteriaceae*, *Pseudomonadaceae*, *Staphylococcaceae*, *Bacillaceae*, *Listeriaceae*, *Campylobacter jejuni*, *Corynebacterium xerosis* and *Candida albicans in vitro* experiments.

MATERIALS AND METHODS

The research was conducted at the laboratories of the "Innovative Technologies and Safety and Quality of Livestock Products" and "Veterinary Pharmacy" of the Department of Veterinary Expertise, Microbiology, Zoohygiene, Safety and Quality of Livestock Products at the Faculty of Veterinary Medicine of Sumy National Agrarian University. The antibacterial activity of the plant tincture was determined by the disk diffusion method in agar using daily cultures of reference strains of microorganisms: *Enterococus faecalis* ATCC No. 19433, *Enterobacter aegorenes* 10006, *Escherichia coli* (F 50) ATCC No. 25922, *Escherichia coli* 055 K 59 No. 3912/41, *Proteus vulgaris* HX 19 No. 222, *Proteus mirabilis* HISK 160208, *Salmonella typhimurium* 144, *Salmonella adobraco* 1, *Klebsiella pneumoniae*, *Yersinia enterocolitica*, *Serratia marcescens* 1, *Pseudomonas aeruginosa* ATCC No. 2853 (F), *Pseudomonas aeruginosa* 27/99, *Campylobacter jejuni*, *Staphylococcus epidermidis* ATCC No. 14990, *Staphylococcus aureus* ATCC No. 25923, *Bacillus subtilis* ATCC No. 6633, *Bacillus cereus* ATCC No. 10702, *Listeria innocua* ATCC No. 33090, *Listeria monocytogenes* ATCC No. 19112, *Listeria ivanovi*, *Corynebacterium xerosis* 1911, *Candida albicans in vitro* experiments.

For this purpose, suspensions were prepared according to the standard for bacterial turbidity of 0.5 McFarland density units (McF) 1.5 × 10^8 CFU, which were determined using a densitometer. The obtained suspensions were streaked on Mueller-Hinton agar (Himedia).

Then, disks soaked with extracted *Ginkgo biloba* tincture were placed, and tetracycline, ciprofloxacin, levomycetin, and azithromycin (5 discs of 30 μg levomycetin; 30 μg azithromycin) were used as positive controls for comparison. Discs with 15.0 μg amphotericin B were also used as the second control against *Candida albicans*. Petri dishes were incubated for 24 hours.

After 24 hours, the diameter of the growth inhibition zone was measured using an Antibiotic Zone Scale-C ruler-template for measuring the sizes of microbial growth inhibition zones (model RW297, India) and TpsDig2 software (Rohlf, 2017). The analysis of *Ginkgo biloba* extract on *P. caudatum* was conducted according to commonly accepted methods (Kotsumbas et al., 2006). The portion of Ginkgo biloba extracts used and the most important information about their antibacterial activity are presented in Family *Ginkgoaceae*, Species *Ginkgo biloba* L. The portion of the plant used LF (Maltas et al., 2011). The results of the conducted research were statistically analyzed using the Fisher-Student method, taking into account the mean values and their standard errors, as well as determining the reliability of comparative indicators.

RESULTS AND DISCUSSIONS

When studying the pharmaceutical action of *Ginkgo biloba*, it has been proven that its extract affects metabolic processes in cells, but the question of its antibiotic action remains open (Ye et al., 2018) (Table 1).

Table 1. The antibacterial effect of *Ginkgo biloba* extract on Enterobacteriaceae Strains

№	Strains	Extract *Ginkgo biloba*, mm	Control, mm			
			Tetracycline	Ciprofloxacin	Levomycetin	Azithromycin
1	*Enterococus faecalis* ATCC No. 19433	18.4±1.9	18.7±2.1	18.3±1.6	20.9±2.5	24.8±2.2
2	*Enterobacter aegorenes* 10006	21.7±0.2	0±0	21.3±2.1	20.9±1.6	16.3±1.8
3	*Escherichia coli* (F 50) ATCC No. 25922	31.3±0.3	0±0	32.6±2.9	28.9±2.4	19.5±1.8
4	*Escherichia coli* 055 K 59 No. 3912/41	34.5±0.3	0±0	26.3±2.4	22.9±2.2	15.3±1.3
5	*Proteus vulgaris* HX 19 No. 222	18.6±0.9	0±0	16.3±1.4	21.9±2.4	0±0
6	*Proteus mirabilis* HISK 160208	10.6±0.2	10.8±1.3	29.3±2.6	15.8±1.2	0±0
7	*Salmonella typhimurium* 144	22.2±0.2	16.3±1.5	35.5±3.8	22.9±2.6	23.8±2.5
8	*Salmonella adobraco* 1	20.1±0.3	4.3±0.3	39.3±3.6	27.9±3.3	26.8±2.7
9	*Klebsiella pneumoniae*	25.5±2.8	0±0	16.3±1.4*	21.9±2.4	0±0
10	*Yersinia enterocolitica*	19.2±0.8	0±0	25.9±2.4	0±0	12.3±1.7
11	*Serratia marcescens* 1	21.6±1.3	33.7±2.7	37.3±3.6	12.8±1.5	0±0

* $P < 0.05$ compared to the control group

Its antioxidant action has been demonstrated (Maltas et al., 2011; Murray, 2013), suggesting the presence of antibacterial action of *Ginkgo biloba* extract. A series of studies were conducted, establishing a high antibacterial effect of *Ginkgo biloba* extract on microorganisms of the *Enterobacteriaceae* family: the most sensitive microorganisms were *Escherichia coli* 055 K 59 No. 3912/41 – 34.5±0.3 mm, while this microorganism was not sensitive to tetracycline, and its sensitivity to ciprofloxacin, levomycetin, and azithromycin was 26.3±2.4, 22.9±2.2, and 15.3±1.3 mm, respectively.

The sensitivity of *Escherichia coli* (F 50) ATCC No. 25922 to *Ginkgo biloba* extract is 31.3±0.3 mm, but it is not sensitive to tetracycline. The lowest level of sensitivity was observed in isolates of *Proteus mirabilis* HISK 160208 and *Proteus vulgaris* HX 19 No. 222 - 10.6±0.2 and 18.6±0.9, respectively. *Salmonella typhimurium* 144 and *Salmonella adobraco* 1 showed moderate sensitivity - 22.2±0.2 and 20.1±0.3, respectively.

Similar sensitivity was observed in *Klebsiella pneumoniae* (25.5±2.8), *Yersinia enterocolitica* (19.2±0.8), and *Serratia marcescens* 1 (21.6±1.3). However, *Yersinia enterocolitica* is not sensitive to tetracycline and levomycetin. *Enterococcus faecalis* ATCC No. 19433 exhibited growth inhibition of 18.4±1.9 mm, while *Enterobacter aegorenes* 10006 showed 21.7±0.2 mm. It can be concluded that microorganisms of the *Enterobacteriaceae genus* exhibit varying degrees of sensitivity to the action of *Ginkgo biloba* extract

The results of the influence of the investigated phytopreparation on strains of *Pseudomonas aeruginosa* (Table 2) were ambiguous: ranging from high inhibition of *Pseudomonas aeruginosa* ATCC No. 2853 (F) (with only a 7.6 mm smaller inhibition zone compared to ciprofloxacin) to weak antibacterial effect on *Pseudomonas aeruginosa* 27/99 (inhibition zone radius of 4.1 mm), with other antibiotics showing no effectiveness (0±0). A moderate inhibitory effect of the *Campylobacter jejuni* extract (8.4 mm) was noted, with no antibiotic exhibiting growth delay of the strain (0±0).

Table 2. The antibacterial effect of *Ginkgo biloba* extract on strains of microorganisms of the *Pseudomonadaceae* family and *Campylobacter jejuni*

№	strains	Extract *Ginkgo biloba*, mm	Control, mm			
			Tetracycline	Ciprofloxacin	Levomycetin	Azithromycin
1	*Pseudomonas aeruginosa ATCC No. 2853 (F)*	21.3±2.1	0±0	28.9±2.7	0±0	0±0
2	*Pseudomonas aeruginosa* 27/99	4.1±0.3	0±0	35.9±2.9	0±0	0±0
3	*Campylobacter jejuni*	8.4±0.9	0±0	0±0	0±0	0±0

It has been shown that *Ginkgo biloba* extract exhibits moderate antibacterial effects against *Staphylococcus epidermidis* and *Staphylococcus aureus* (inhibition zone diameter of 8.7 mm and 10.8 mm, respectively) with a high degree of inhibition compared to the antibiotic control groups.

A variable effect was observed on microorganisms of the *Bacillaceae* family, ranging from a higher antibacterial effect on *Bacillus subtilis* (inhibition zone diameter of 14.7 mm) to a moderate effect on *Bacillus cereus* (5.9 mm).

Ginkgo biloba extract demonstrates a high antibacterial effect on *Listeria innocua* and *Listeria monocytogenes* (with inhibition zone diameters of 19.7 mm and 10.4 mm, respectively). *Listeria ivanovi* showed resistance to the studied phytopreparation (no inhibition observed, 0 mm).

It should be noted that there is antibiotic resistance in the strain of *Listeria monocytogenes* to tetracycline, ciprofloxacin, and azithromycin (0 mm inhibition observed) (Table 3).

Table 3. The antibacterial effect of extract of *Ginkgo biloba* on cryogenic strains of *Staphylococcaceae*, *Bacillaceae*, *Listeriaceae* microorganisms

№	Strains	Inhibition zone diameter, mm	Control, mm			
			Tetracycline	Ciprofloxacin	Levomycetin	Azithromycin
1	*Staphylococcus epidermidis* ATCC No. 14990	8.7±0.8	28.7±3.3	28.3±2.9	25.9±1.8	11.8±1.1
2	*Staphylococcus aureus* ATCC No. 25923	10.8±0.9	25.7±2.8	21.3±2.5	22.9±2.2	20.9±2.5
3	*Bacillus subtilis* ATCC No. 6633	14.7±1.3	35.7±2.8	36.3±3.5	28.9±3.2	31.8±3.7
4	*Bacillus cereus* ATCC No. 10702	5.9±0.8	27.7±2.3	12.3±0.9	22.9±2.5	16.8±1.5
5	*Listeria innocua* ATCC No. 33090	19.7±1.3	27.7±2.7	20.3±2.1	18.9±1.6	27.8±3.2
6	*Listeria monocytogenes* ATCC No. 19112	10.4±1.3	0±0	0±0	22.9±2.33	0±0
7	*Listeria ivanovi*	0±0	27.9±2.3	35.9±2.9	26.8±2.7	16.3±1.4

A low antibacterial effect was observed from the application of ethanol extract of *Ginkgo biloba* on strains of *Corynebacterium xerosis* (inhibition zone diameter 2.3 mm) and *Candida albicans* (1.2 mm). *Corynebacterium xerosis* exhibited resistance to tetracycline (0±0), while *Candida albicans* showed resistance to all control antibiotics (0±0) (Table 4).

Table 4. Antibacterial effects of extracts of *Ginkgo biloba* on cryogenic strains of microorganisms of the *Corynebacterium xerosis* and *Candida albicans*

№	strains	Inhibition zone diameter, mm	Control, mm			
			Tetracycline	Ciprofloxacin	Levomycetin	Azithromycin
1	*Corynebacterium xerosis* 1911	2.3±0.2	0±0	16.7±1.5	21.9±2.4	11.8±1.1
2	*Candida albicans*	1.2±0.2	0±0	0±0	0±0	0±0

CONCLUSIONS

The in vitro experiment demonstrated a favorable antibacterial effect resulting from the application of *Ginkgo biloba* extracts on strains of various microorganisms including *E. faecalis*, *P. vulgaris*, S. *marcescens*, *Y. enterocolitica*, *K. pneumoniae*, *P. aeruginosa*, *C. jejuni*, *S. epidermidis*, *S. aureus*, *B. subtilis*, *L. innocua*, and *L. monocytogenes*. We suggest further investigation of these *Ginkgo biloba* extracts for combating multidrug-resistant strains of the mentioned microorganisms. The ethanol extract of *Ginkgo biloba* is classified as moderately toxic during biotesting on *P. caudatum*, with an LC50 corresponding to a 0.3% concentration of the preparation. This study was supported by the Ministry of Education and Science of Ukraine (grant 0117U006533).

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