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EXPLORING THE MEDICINAL POTENTIAL OF INVASIVE PLANTS: IMPACT ON CELLULAR AND EXTRACELLULAR GLUTATHIONE–S–TRANSFERASE ACTIVITY

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ABSTRACT

Invasive alien species threaten ecosystems but can offer medicinal benefits. This study explores the therapeutic potential of the invasive plant species Ailanthus altissima *(Mill.) Swingle,* Helianthus tuberosus *L.,* Robinia pseudoacacia *L., and* Solidago canadensis *L. by analysing the effects of their ethanolic leaf and flower extracts (0.1, 0.5, 1 mg/mL) on glutathione S-transferase (GST) activity in HEPG2 cells and culture media. The catalytic activity of the enzyme was measured spectrophotometrically after 24 hours of cell treatment with extracts by monitoring the change in*

absorbance at 340 nm during the conjugation of L-glutathione with 1-chloro-2,4-dinitrobenzene (CDNB), a universal substrate for GST. The extracts modulated GST activity in both cellular lysates and extracellular media. GST activity in cell lysates decreased with increasing concentrations of A. altissima *flower and* R. pseudoacacia *leaf extracts. Similarly, media samples exposed to all tested extracts showed reduced GST activity at higher concentrations, indicating a potential inhibitory effect. Conversely,* R. pseudoacacia *flower and* S. canadensis *leaf extracts increased GST activity in lysates at 0.5 and 1 mg/mL. These concentration-dependent fluctuations suggest complex interactions between plant compounds and GST, likely influenced by phenolic compounds such as ellagic acid and quercetin, known non-competitive GST inhibitors. Such inhibition may enhance the accumulation of toxic metabolites in cancer cells, increasing their vulnerability. This study highlights the therapeutic potential of invasive plant species and their specialised metabolites, opening avenues for further exploration of their role in regulating GST activity and their application in cancer treatment strategies.*

Keywords: *antitumor activity, invasive species, plant extracts, phytopharmaceuticals*

1. INTRODUCTION

Invasive alien plant species have been introduced to a new area outside their natural habitat and exhibit rapid adaptation to the conditions of the new environment, exceptional capacity for rapid, autonomous reproduction, as well as high abundance and density (Pejchar, Mooney, 2009). These traits make them readily available for various applications, including research into their medicinal properties.

The medicinal properties of plants have been a cornerstone of traditional and scientific medicine for centuries. Invasive species, with their unique chemical compositions and biological activities, present untapped potential for therapeutic research (Macel et al., 2014; Bravo et al., 2021). Notably, these plants contain high concentrations of phenolic compounds, such as ellagic acid, quercetin, and chlorogenic acid, known for their anticancer, antioxidant, and anti-inflammatory properties (Sahu, Devkota, 2016; Lopez-Corona et al., 2022). Phenolic extracts from these plants may also influence key enzymatic activities, such as those of glutathione S-transferases (GSTs), a family of enzymes essential for detoxification and drug metabolism (Mazari et. al 2023). GSTs catalyse the nucleophilic attack of reduced glutathione (GSH) on non-polar compounds containing an electrophilic carbon, nitrogen, or sulphur atom (Hayes, Pulford, 1995). Substrates include a wide range of xenobiotics, such as various drugs, pesticides, carcinogens, and pollutants, as well as endogenous compounds like α,β-unsaturated aldehydes, quinones, epoxides, and hydroperoxides, which are secondary metabolites formed during oxidative stress. Through conjugation with GSH, substrates are inactivated and typically transformed into hydrophilic derivatives, which can be more easily eliminated from the body via urine or bile.

Particularly noteworthy are GSTs present in tumor cells, which exploit the detoxification and protective effects of GSTs for their development and survival. Among other mechanisms, GSTs bind to drugs used in cancer therapy and convert them into less active forms, thereby preventing them from exerting their intended effects (Mazari et al., 2023). Elevated GST

levels have been observed in various cancers, including melanoma (Carretero et al., 1999). Consequently, GST inhibitors have emerged as a new area of interest in antitumor therapy, as they enhance the sensitivity of tumor cells to anticancer drugs.

Some invasive plant species contain a high concentration of phenolic compounds, such as ellagic acid and quercetin, which are known to reduce GST activity (Čižmárikova et al., 2023). Such properties could make them valuable in natural antioxidant therapies, particularly for mitigating GST-related oxidative stress in diseases like cancer.

Our previous studies (Poljuha et al., 2017, 2022) highlighted invasive species in Croatia as valuable sources of phenolics with antioxidant and antimicrobial properties. This study focuses on the potential antitumor activity of four invasive alien plant species widespread in Croatia: *Ailanthus altissima* (Mill.) Swingle, *Helianthus tuberosus* L., *Robinia pseudoacacia* L., and *Solidago canadensis* L. *R. pseudoacacia* (black locust) is particularly rich in phenolics, such as epigallocatechin, ferulic acid, hyperoside, and rutin, known for their antioxidant, antimicrobial, anticancer, and neuroprotective effects (Uzelac et al., 2023). Similarly, *A. altissima* (tree of heaven), *H. tuberosus* (Jerusalem artichoke), and *S. canadensis* (Canada goldenrod) produce specialised metabolites with antioxidant, anti-inflammatory, and antimicrobial activities (Saiki et al., 2022; Rolnik, Olas, 2021). Traditionally, these species have been used for diuretic, spasmolytic, and wound-healing purposes (Apáti et al., 2003).

While posing ecological threats, these four invasive species also offer opportunities for pharmaceutical development due to their rapid growth, wide availability, and diverse bioactive profiles (Sladonja et al., 2018). This study aims to evaluate the effects of ethanolic extracts from the leaves and flowers of these plants on GST activity in both cellular lysates and extracellular environments. The hypothesis is that these extracts, at varying concentrations, can modulate GST activity, thereby contributing to developing novel therapeutic approaches.

2. MATERIALS AND METHODS

2. 1 Plant material

Leaves and inflorescences from the four analysed species (*A. altissima*, *H. tuberosus*, *R. pseudoacacia*, and *S. canadensis*) were collected between June and September 2022 in the Istria region of Croatia. A total of 15 samples from every species were obtained from five distinct locations (three samples per site), spanning latitudes from N45.4073056 to N44.8461944. After harvesting, the plant material was air-dried in the shade at room temperature. Before grinding, the individual flowers were separated from the inflorescences. Approximately 250 g of dry plant material from every location was pooled to obtain a representative sample for the research area. The material was finely minced using a Grindomix GM 200 knife mill (Retsch, Haan, Germany) programmed at 10,000 rpm/30 s, stored in plastic bags, vacuumed and stored at +4°C until analysis.

2. 2 Extraction procedure

Dried and ground plant material (10 g) was dissolved in 100 mL of 70% ethanol and shaken at room temperature for 15 minutes at 150 rpm using a shaker-incubator (lES-20, Biosan Medical-Biological Research & Technologies Company, Latvia). Samples were sonicated for 30 minutes at 30°C and centrifuged for 5 min at 3500 rpm (Jouan MR23i, Jouan S.A., Saint-Herblain, France), filtered through 0.45 µm polytetrafluoroethylene (PTFE) filters (Macherey-Nagel, Düren, Germany). Afterwards, the samples were concentrated in diethyl ether using BUCHI R-300 Rotavapor (BÜCHI Labortechnik AG, Flawil, Switzerland) at 40°C and stored at +4°C until analysis.

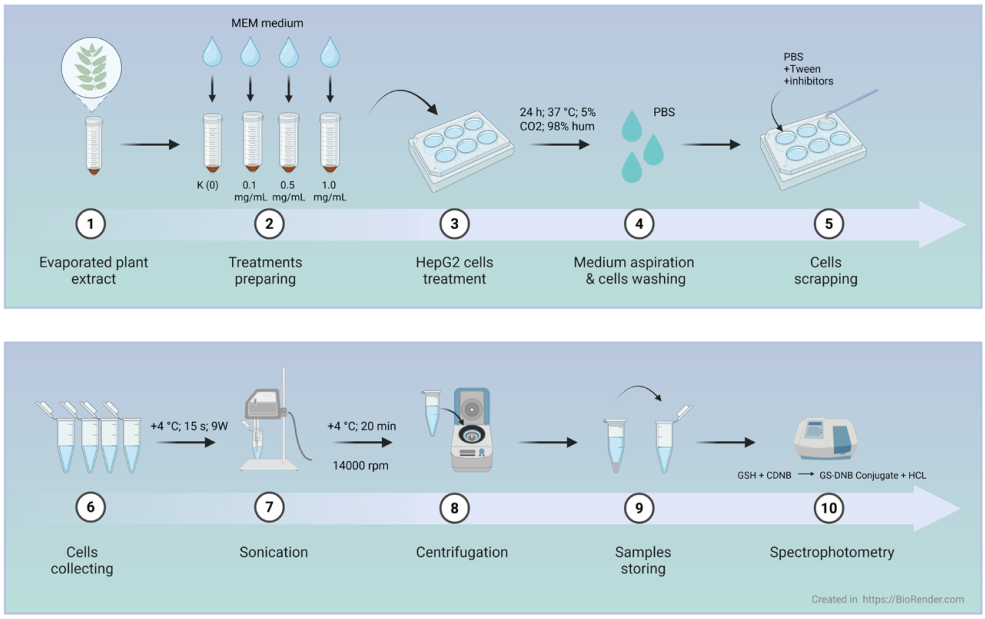
2. 3 Cell cultivation

For this study, human hepatoblastoma HepG2 cells were used. The HepG2 cells were cultured in a complete Minimum Essential Medium (MEM), supplemented with sodium pyruvate (1 mM/L) and 10% Fetal Bovine Serum (FBS), in an incubator set at 37°C with 5% CO_2 and 98% relative humidity. Once the cells reached approximately 80% confluence, they were transferred into six-well plates. At 80% confluence, the medium was removed, and the cells were washed with phosphate-buffered saline (PBS), which was subsequently aspirated in the same manner as the medium.

2. 4 Cell treatment with extracts of invasive plant species

In this study, the effects of ethanolic extracts from the leaves and flowers of invasive plant species on GST catalytic activity were examined at various concentrations. Evaporated ethanolic extracts from tree of heaven, Jerusalem artichoke, black locust, and Canadian goldenrod were prepared at concentrations of 0.1 mg/mL, 0.5 mg/mL, and 1.0 mg/mL in a MEM medium, which is also used as a control. The HepG2 cells were plated in six-well plates and incubated for 24 hours with prepared extracts under standard conditions (37°C, 5% CO_2, and 98% relative humidity). Following incubation, the medium was aspirated and stored for subsequent GST catalytic activity measurement, and the cells were rinsed with phosphate-buffered saline (PBS), which was subsequently removed by the same method. Next, 500 µL of a PBS solution containing Tween, protease, and phosphatase inhibitors were added to each well. Cells were scraped and collected into Eppendorf tubes kept on ice. An additional 500 µL of PBS + Tween mixture was used to collect any remaining cells, and these were also transferred to the same Eppendorf tubes. Cell samples were then sonicated for 15 seconds on ice at 4°C at an ultrasonic homogeniser intensity of 9 W. Post-sonication, the samples were centrifuged at 14,000 rpm for 20 minutes at 4°C. The supernatant was transferred to new tubes and stored at -80 °C for the analysis of GST catalytic activity (Figure 1).

Figure 1. Cell treatment with extracts of invasive plant species



Measurement of enzymatic activity was performed spectrophotometrically on a semi-automatic biochemical analyser Trace 300 at 340 nm using Glutathione S-Transferase (GST) Assay Kit (Catalog Number CS0410, Sigma-Aldrich, St. Louis, MA, USA). The method is based on the reaction of conjugation between L-glutathione and 1-chloro-2,4-dinitrobenzene (CDNB) through the nucleophilic thiol group of glutathione, and the resulting conjugate is absorbed at 340 nm. The rate of increase in absorbance is directly proportional to the activity of GST in the sample. The enzyme's catalytic activity is expressed in micromoles of product formed per millilitre per minute and is calculated using the following formula, as provided by the kit manufacturer:

$$\frac{(\Delta A_{340})/\min \times V(ml) \times dil}{\varepsilon_{mM} \times V_{enz}(ml)} = \mu mol/ml/\min$$

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dil = dilution factor of the initial sample (1)

ε_{mM} = molar extinction coefficient for the CDNB conjugate at 340 nm (9.6 mM^{-1}; path length 1 cm)

V (mL) = reaction volume (1 mL)

V_{enz} = sample volume (50 x 10^3 nL)

To determine the specific catalytic activity of the enzyme, the measured catalytic activity is divided by the protein concentration. The total protein concentrations are measured using a

spectrofluorometer at 280 nm and are expressed in mg/mL. The presented catalytic activities of the enzyme in the medium from the treated cells represent the normalisation of the measured catalytic activities in the medium to the unit concentration of total protein in the corresponding lysate samples.

2. 5 Statistical Analysis

A one-way analysis of variance (ANOVA) with post hoc Tukey's test was used to assess significant differences in GST activity in different cell treatments. Statistical significance was determined with *p*-values equal to or less than 0.05. In the table representations, distinct letters indicate significant differences among values.

3. RESULTS AND DISCUSSION

Glutathione S-transferase (GST) activity was analysed in 192 samples: 48 cell lysates exposed to leaf extracts and 48 to flower extracts (control and three concentrations) from four invasive plant species (*Ailanthus altissima, Helianthus tuberosus, Robinia pseudoacacia*, and *Solidago canadensis*). Additionally, 96 culture media samples from these treatments were analysed.

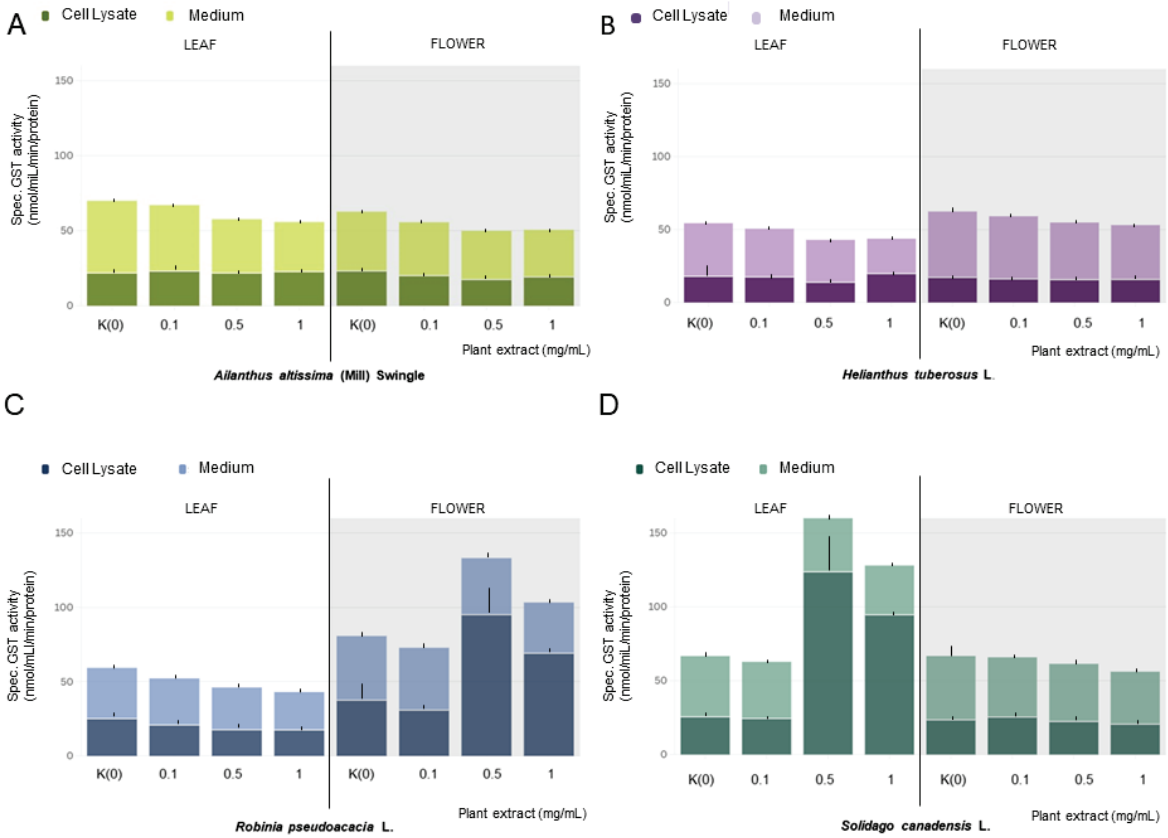
Table 1 summarises the specific GST activity in Hep G2 cell lysates and culture media after 24 hours of treatment with extract concentrations of 0.1 mg/mL, 0.5 mg/mL, and 1 mg/mL, along with controls. For a better insight into the complete analysis, all specific GST activities are also shown graphically, by plant species (Graph 1A-D). The study evaluated the effects of ethanolic extracts from invasive plant leaves and flowers on GST activity in cell lysates and extracellular media. The focus was to compare GST activity in treated versus control samples (K0) without directly comparing plant species or lysates and media. The results revealed that extracts from all species influenced GST activity (Table 1, Graph 1).

Specifically, both leaf and flower extracts of *A. altissima* decreased GST activity in media. Flower extracts also reduced GST activity in lysates (Graph 1A). The leaf extracts of *H. tuberosus* reduced GST activity in both lysates and media, while flower extracts affected GST activity in media at higher concentrations (Graph 1B). However, at a concentration of 1.0 mg/mL, there was a noticeable increase in activity in the cell lysates treated with the extract, indicating a potential concentration-dependent effect that may differ between cellular and extracellular environments. *R. pseudoacacia* leaf extracts reduced GST activity in both lysates and media, while flower extracts strongly increased GST activity in lysates but decreased it in media at higher concentrations (Graph 1C). A similar effect was observed in *S. canadensis* leaf extracts (Graph 1D), which might suggest an induction mechanism through certain compounds within the extract. The highest enzymatic activity in the medium above cells treated with the flower extract of *S. canadensis* was observed at 0.1 mg/mL, with a decrease in activity at higher concentrations, indicating a concentration-dependent inhibition of GST release into the medium. This pattern highlights a concentration-dependent fluctuation in the enzyme's activity in both cellular and extracellular environments.

Table 1. Specific GST activity (nmol/ml/min/protein) in HepG2 cell lysates and culture media after 24 hours of treatment with plant extracts. Values represent the mean ± standard deviation (SD) of three replicates. Different letters in the same row indicate significant differences in specific GST activity between different treatments in the cell lysate (A-C) and media (a-c) (ANOVA, Tukey's test); *–statistically significant differences at p-value ≤ 0.05).

Species	Plant organ		Spec. GST activity (nmol/ml/min/protein)							
			Cell lysate				Medium			
		Treatment	Control (0 mg/mL)	0.1 mg/mL	0.5 mg/mL	1 mg/mL	Control (0 mg/mL)	0.1 mg/mL	0.5 mg/mL	1 mg/mL
Ailanthus altissima	Leaf	Mean	21.76	23.06	21.72	22.66	48.19	44.03	35.97	33.19
		SD	1.11	1.37	1.52	0.76	1.27	1.97	1.58	3.39
		*	A	A	A	A	a	a	b	b
	Flower	Mean	23.14	19.99	17.46	19.19	39.58	35.69	32.5	31.39
		SD	1.3	2.43	0.85	0.71	1.82	1.05	0.72	1.27
		*	A	B	B	AB	a	b	bc	c
Helianthus tuberosus	Leaf	Mean	17.98	17.53	13.91	19.86	36.39	33.06	29.03	23.89
		SD	4.99	2.05	0.39	1.90	0.24	0.24	1.03	1.34
		*	B	B	C	A	a	ab	ab	b
	Flower	Mean	17.23	16.18	15.67	15.83	45.14	42.92	39.17	37.22
		SD	0.12	1.27	0.75	1.76	2.44	1.50	1.50	1.68
		*	A	A	A	A	a	a	b	b
Robinia pseudoacacia	Leaf	Mean	25.09	20.80	17.60	17.48	34.17	31.39	28.47	25.56
		SD	0.47	0.73	1.33	1.44	2.60	2.64	2.68	1.68
		*	A	B	C	C	a	ab	ab	b
	Flower	Mean	37.52	30.85	95.08	69.09	43.19	41.94	38.06	34.17
		SD	10.06	2.26	18.09	3.05	0.64	2.06	0.87	2.21
		*	B	B	A	A	a	ab	bc	c
Solidago canadensis	Leaf	Mean	25.54	24.44	123.70	94.64	41.11	38.33	38.06	34.17
		SD	2.27	2.33	19.36	2.61	3.39	1.50	2.74	1.10
		*	C	C	A	B	a	ab	ab	b
	Flower	Mean	23.51	25.40	22.35	20.55	43.19	40.42	39.03	35.56
		SD	3.65	1.62	4.12	2.79	0.64	0.83	1.88	1.58
		*	A	A	A	A	a	ab	bc	c

Graph 1. Specific GST activity (nmol/ml/min/protein) in HepG2 cell lysates and culture media after 24 hours of treatment with plant extracts in concentrations ranging from 0.1 mg/mL to 1.0 mg/mL, compared to the control (K0) 24 hours of treatment with plant extracts. The effects of plant extracts of f our invasive plant species were tested: A) *Ailanthus altissima* (Mill.) Swingle; B) *Helianthus tuberosus* L.; C) *Robinia pseudoacacia* L.; D) *Solidago canadensis* L.



The effects of invasive plant extracts on GST activity in a tumor cell line, varying with concentration and plant part, likely involve phenolic compounds like ellagic acid, a known concentration-dependent GST inhibitor. Ellagic acid, a natural phenolic compound present in analysed invasive plant species (Poljuha et al., 2022) with well-documented anticancer properties, exerts multiple effects on colorectal cancer (CRC) cells, notably inhibiting cell proliferation, inducing apoptosis, and causing cell cycle arrest, specifically in HCT-116 CRC cell lines (Zhao et al., 2023). Ellagic acid's anticancer effects are associated with the differential expression of certain long noncoding RNAs (lncRNAs), which play crucial roles in regulating cellular processes relevant to tumorigenesis and cancer progression. Specifically, following ellagic acid treatment, 206 lncRNAs with altered expression (115 down-regulated and 91 up-regulated) were identified, suggesting that ellagic acid may influence gene expression networks critical for its anti-proliferative and pro-apoptotic effects in CRC cells. These findings contribute to understanding ellagic acid's potential as a chemo-preventive agent and indicate its involvement in regulatory pathways that might also modulate GST (glutathione S-transferase) enzyme activity. Given the known inhibitory action of certain phenolic compounds, including ellagic acid and quercetin, on GST activity, it is plausible that the observed reduction in GST activity in HepG2 cells treated with phenol-rich plant extracts may be attributed to similar interactions. GSTs, key detoxifying enzymes, play a protective role in cellular response to oxidative stress and xenobiotics. Inhibiting GST activity with phenolic compounds could have therapeutic implications, particularly in cancer treatment strategies aimed at reducing the detoxification of chemotherapeutic agents by cancer cells. Such inhibition might enhance the efficacy of anticancer agents by allowing higher intracellular retention of these compounds, while also potentially contributing to increased oxidative stress within cancer cells. Further studies are warranted to analyse the precise phenolic composition of these plant extracts, with an emphasis on compounds like ellagic acid, quercetin, and other polyphenols, to elucidate their specific roles in modulating GST activity. Investigating the concentration-dependent effects and cellular mechanisms of GST inhibition could shed light on the potential of these extracts as natural inhibitors of GST, thereby broadening their application as complementary agents in cancer therapeutics.

4. CONCLUSION

The data shows that ethanolic leaf and flower extracts from invasive plant species both inhibit and induce GST activity, suggesting complex interactions with plant compounds, likely influenced by phenolic compounds as non-competitive inhibitors. Variations in GST activity across concentrations and plant parts highlight the need for broader dose-response studies to determine optimal inhibitory or inducing effects. Further research into the phenolic profiles of these extracts and their specific interactions with GST is essential for assessing their potential as complementary agents in cancer treatment. The study also reveals changes in GST activity in culture media and cell lysates after treating HepG2 cells with these extracts, raising questions about the active compounds and underlying mechanisms. These insights could help evaluate the phytopharmaceutical potential and antitumor properties of invasive plant extracts.

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ISTRAŽIVANJE LJEKOVITOG POTENCIJALA INVAZIVNIH BILJAKA: UTJECAJ NA STANIČNU I IZVANSTANIČNU AKTIVNOST GLUTATION-S-TRANSFERAZE

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SAŽETAK

*Invazivne strane vrste predstavljaju prijetnju ekosustavima ali imaju i ljekovita svojstva. Ova studija istražuje terapijski potencijal invazivnih biljnih vrsta – pajasena (*Ailanthus altissima *(Mill.) Swingle), čičoke (*Helianthus tuberosus *L.), običnog bagrema (*Robinia pseudoacacia *L.) i kanadske zlatošipke (*Solidago canadensis *L.) - analizom učinaka etanolnih ekstrakata lista i cvijeta ovih vrsta u tri koncentracije (0,1, 0,5, 1 mg/mL) na aktivnost glutation S-transferaze (GST) u staničnim lizatima i mediju iznad HEPG2 stanica. Katalitička aktivnost enzima mjerena je spektrofotometrijski nakon 24h tretmana stanica ekstraktima, praćenjem promjene apsorbancije na 340 nm tijekom konjugacije*

L-glutationa s 1-kloro-2,4-dinitrobenzenom (CDNB), univerzalnim supstratom za GST. Rezultati su pokazali da tretman ovim ekstraktima utječe na aktivnost GST u staničnom lizatu i u izvanstaničnom okruženju. Katalitička aktivnost u staničnim lizatima smanjivala se s povećanjem koncentracije etanolnih ekstrakata cvjetova A. altissima *i listova* R. pseudoacacia *te u hranjivom mediju iz kultura izloženih ekstraktima listova i cvjetova svih analiziranih vrsta, što ukazuje na potencijalni inhibitorni učinak testiranih ekstrakata. Nasuprot tome, ekstrakti cvijeta* R. pseudoacacia *i lista* S. canadensis *povećali su aktivnost GST u lizatima pri koncentracijama 0,5 i 1 mg/mL. Ove fluktuacije ovisne o koncentraciji sugeriraju složene interakcije između biljnih metabolita i GST, na koje vjerojatno utječu fenolni spojevi kao što su elaginska kiselina i kvercetin, poznati nekompetitivni inhibitori GST. Takva inhibicija može pojačati nakupljanje toksičnih metabolita u tumorskim stanicama, povećavajući njihovu ranjivost. Ova studija naglašava terapeutski potencijal invazivnih biljnih vrsta i njihovih specijaliziranih metabolita, otvarajući puteve za daljnje istraživanje njihove uloge u regulaciji aktivnosti GST i njihovu primjenu u strategijama liječenja raka.*

Ključne riječi: *antitumorsko djelovanje, invazivne vrste, biljni ekstrakti, fitofarmaceutici*