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THE MODULATORY ACTION OF *TARAXACUM OFFICINALE* ON THE GLUTATHIONE SYSTEM

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Summary.

The evaluation of the antioxidant activity of plants has been an important issue taking into account its importance on human health. Natural antioxidants protec t cells against oxidative stress, which can damage the cellular components. *Taraxacum officinale* (TO) leaves (TOL) and roots (TOR) has been commonly used in traditional medicine due to biologically active ingredients. This plant is rich in substances with high antioxidant activity (flavonoids, phenolic acids, coumarins, vitamins etc.). Glutathione represents the most abundant thiol of cells with important functions in the antioxidant system. Until now, there are no comprehensive data about TO extracts action on glutathione content.

The objective of the study was to report the influence of TOL and TOR ethanolic extracts on the glutathione content of erythrocytes. TOL and TOR were harvested from a natural habitat of Republic of Moldova. The dry plants were extracted using ethanol as solvent (10, 20, 25, 40, 50 and 80% (v/v)). As source of glutathione were red blood cells (RBC) of healthy persons. As a result we determined that TO exhibits a modulatory action on glutathione content. The highest (28.03±1.14 μM/g. Hb) content of GSH was determined due to action of roots extracts made on ethanol of 20%, the lowest (10.88±0.83 μM/g. Hb) in case of leaves extracted on alcohol of 20%. Opposite, the lowest (5.92±0.72 μM/g. Hb) amount of GSSG was determined as a result of action of radicular extracts made on ethanol of 20%. The highest (11.46±3.27 μM/g. Hb) concentration of GSSG was determined by influence of roots extracts on ethanol of 50%.

In conclusion, *Taraxacum officinale* exhibits a strong antioxidant activity. This plant has ability to prevent and treat the damage of cells caused by oxidative stress process, by actioning on glutathione system. This activity depends of ethanol concentrations and plant's part.

Key words: glutathione, *Taraxacum officinale* roots and leaves, red blood cells, antioxidants.

Rezumat: Acțiunea modulatorie a *Taraxacum officinale* asupra sistemului glutationic.

Evaluarea activității antioxidante a plantelor a fost mereu de o importanță majoră pentru știință. Antioxidanții naturali protejează celulele contra stress-ului oxidativ, care poate afecta componentele celulare. Frunzele și rădăcinile de *Taraxacum officinale* (TO) sunt utilizate în medicina tradițională datorită ingredientelor sale biologic active. Această plantă este bogată în substanțe cu activitatea antioxidantă înaltă (flavonoizi, acizi fenolici, cumarine, vitamine etc.). Glutationul reprezintă unul din cei mai abundenți tioli ai celulelor exercitând funcții importante în cadrul sistemului antioxidant. Până în prezent însă, nu există date exhaustive referitor la acțiunea extractelor din TO asupra conținutului de glutation.

Scopul acestui studiu a fost de a determina influența extractelor etanolice din frunze și rădăcini de TO asupra conținutului de glutation eritrocitar. TO au fost recoltate dintr-un mediu natural al Republicii Moldova. Plantele uscate au fost supuse extracției pe etanol de diverse concentrații (10, 20, 25, 40, 50 și 80% (v/v)). În calitate de sursă de glutation au servit eritrocitele persoanelor sănătoase. În rezultatul acestui studiu am determinat că, TO posedă acțiune modulatorie asupra conținutului de glutation. Conținutul cel mai înalt de GSH (28.03±1.14 μM/g. Hb) a fost determinat ca urmare a acțiunii extractului radicular pe etanol de 20%, iar cel mai mic (10.88±0.83 μM/g. Hb) în cazul extractului foliar pe alcool de 20%. Opus, cea mai mică concentrație de GSSG (5.92±0.72 μM/g. Hb) a fost determinată ca urmare a acțiunii extractului radicular pe etanol de 20%, iar cel mai înalt conținut de GSSG (11.46±3.27 μM/g. Hb) a fost raportat după acțiunea extractului din rădăcini pe etanol de 50%.

În concluzie, *Taraxacum officinale* posedă activitate antioxidantă promițătoare. Această plantă are abilitatea de a preveni și trata lezarea celulelor produsă în cazul stress-ului oxidativ, prin acțiunea asupra sistemului glutationic. Activitatea antioxidantă a TO depinde de concentrația etanolului și partea componentă a plantei.

Cuvinte cheie: glutation, frunze și rădăcini de *Taraxacum officinale*, eritrocite, antioxidanți.

Резюме: Модуляторное воздействие *Taraxacum officinale* на глутатионовую систему.

Оценка антиоксидантной активности растений всегда имела большое значение для науки. Природные антиоксиданты защищают клетки от окислительного стресса, который может повредить клеточные компоненты. Листья и корни *Taraxacum officinale* (ТО) используются в народной медицине благодаря своим биологически активным компонентам. Это растение богато веществами с высокой антиоксидантной активностью (флавоноиды, фенольные кислоты, кумарины, витамины и др.). Глутатион — один из самых распространенных тиолов в клетках, выполняющий важные функции в антиоксидантной системе. Однако до настоящего времени отсутствуют исчерпывающие данные о действии экстрактов ТО на содержание глутатиона.

Целью настоящего исследования явилось определение влияния спиртовых экстрактов листьев и корней ТО на содержание глутатиона в эритроцитах. ТО были собраны из природной среды Республики Молдова. Высушенные растения подвергали экстракции этанолом различной концентрации (10, 20, 25, 40, 50 и 80% (об./об.)). Источником глутатиона служили эритроциты здоровых людей. В результате этого исследования мы определили, что ТО оказывает модулирующее действие на содержание глутатиона. Наибольшее содержание GSH (28.03±1.14 мкМ/г Hb) было определено в результате действия экстракта корней на 20% этаноле, а наименьшее (10.88±0.83 мкМ/г Hb) - в случае листового экстракта на 20% спирте. Наоборот, наименьшая концентрация GSSG (5.92±0.72 мкМ/г Hb) определялась в результате действия экстракта корней на 20% этаноле, а наибольшая концентрация GSSG (11,46±3,27 мкМ/г Hb) была определена после воздействия экстракта корней на 50% этаноле.

В заключение, *Taraxacum officinale* обладает многообещающей антиоксидантной активностью. Это растение обладает способностью предотвращать и лечить повреждения клеток, вызванные окислительным стрессом, воздействуя на систему глутатиона. Антиоксидантная активность ТО зависит от концентрации этанола и составной части растения.

Ключевые слова: глутатион, листья и корни одуванчика лекарственного, эритроциты, антиоксиданты.

Introduction.

Glutathione is an antioxidant which prevents the destruction of cellular components by reactive oxygen species (ROS), reactive nitrogen species (RNS), free radicals (FR), peroxides, lipid peroxides and heavy metals [1]. All of these substances can damage the cells components, during a process called as oxidative stress (OS).

Chemically, glutathione represents a tripeptide consisting of glutamic acid (Glu), cysteine (Cys) and glycine (Gly). Its biosynthesis requires 2 enzymes, glutamate–cysteine ligase and glutathione synthetase.

The chemical structure of glutathione determines its functions and distribution among of all living organisms reflects its extremely important biological role. The sulfhydryl group (SH) in the Cys structure serves as a proton donor and is responsible for its biological activity. Glutathione is actively involved in the metabolism of estrogens, leukotrienes and prostaglandins, participates in the reduction of ribonucleotides into deoxyribonucleotides, as well in the maturation of iron-sulfur groups in proteins or transfer of copper and iron, etc [2–6].

Antioxidants represent substances which can stop formation of free radical by giving hydrogen atoms or scavenging them. The reduced glutathione, as well enzymes, glutathione peroxidase (GPOx), glutathione reductase (GR) and glutathione-S-transferase (GST) represent antioxidants which prevent the formation of FR by converting them into less harmful molecules. The SH residue of GSH is a source of one reducing equivalent, in case of thiol protection and redox regulation of cellular thiol proteins under OS action. During this process GSH is converted to its oxidized form (GSSG) glutathione-disulfide also called L-(–)-glutathione. The last, oxidized state in return is converted to the reduced state by nicotinamide adenine dinucleotide phosphate (NADPH), conversion catalyzed by GR [7].

The ratio GSH/GSSG is modified in many conditions of cellular redox imbalance and has been seen to change in many human diseases such as: neurodegenerative disorders, diabetes mellitus type 1 and 2, inflammatory bowel disease, asthma, rheumatoid arthritis, endometriosis, metabolic syndrome, and others. Also GSH is involved in immune functions and in the antimicrobial and antiviral defense of cells [3,8].

Taraxacum officinale (TO) F. H. Wigg or *Dandelion* leaves and roots are natural, cheap and largely available sources, used during centuries for the treatment of various ailments, exhibiting choleretic, diuretic, antirheumatic, anti-inflammatory, appetite-stimulating and laxative properties, used as antidiabetic and antitumor drug [9]. Chemical composition of TOL and TOR is amazing due to: microelements (potassium, iron, calcium, magnesium and phosphorus), vitamins (A, C, B1, B2, etc.), polifenolic compounds (chicoric, 4-caffeoylquinic, chlorogenic, caffeic, p-coumaric, ferulic acids and their derivatives), flavonoids, saponins, essential oils, inulin and proteins [10–12]. Many of these components have promising antioxidant activities [4,13].

Until now, there are no comprehensive data about TO extracts action on glutathione content. Our results

demonstrate that TO possess a great antioxidant activity, which depends of plants part and concentration of extractant.

Materials and methods.

Taraxacum officinaleF. H. Wigg leaves and roots were harvested in May of 2017 from a natural habitat from Republic of Moldova. After cleaning and weighing, the vegetal material was placed in the lab conditions at room temperature, for 2 weeks. Dried leaves and roots were grinded (*Scarlett Coffee grinder SC-4145*) to a fine powder and samples were soaked in 100 mL of ethanol(Luxfarmol, MD) of 80%, 50%, 40%, 25% 20% and 10%. The extractionshave been realized at room temperature for 24 hours, process followed by filtration through Whatman No.1 WHA10010155 (Merck, DE). Aliquots of 1,5ml of every type of extract were centrifuged (MPW 370, during 5 min, at 5000 rpm). The samples purity was confirmed by the absence of stratification and sedimentation.

Healthy persons' blood was diluted 1:4 v/v with DMEM (Dulbecco medium), mixed up with gentamicin (100 µg/ml), heparin (2.5 un/ml) and L-glutamine (0.6 mg/ml). To the diluted blood (0,9 ml), TO extracts (0.1 ml) were added in all test wells, except for the control group, in which the TO extracts were replaced with equivalent amount and concentration of alcohol. After 24 hours of incubation at 37^0C and 3,5% CO_2 humidified atmosphere the microplates were centrifuged for 5 min, at 1500 rpm. The obtained erythrocytes mass (15 µL) was used for further glutathione system assessments. All experiments were done in triplicate in 24-wells microplates.

The influence of TO extracts on RBC's glutathione system (GSSG, GSH and total GSH), was evaluated in accordance with Ryzhikov S.L. *et al.* (2011) method, modified by us [14]. The total amount of the reduced and oxidized forms of glutathione was determined by using a kinetic assay, in which catalytic amounts of GSH or GSSG and GR bring about the continuous reduction of DTNB (5,5′-dithiobis 2-nitrobenzoic acid) by NADPH. All of the methods have been adapted for application to the *Synergy H1 Hybrid Multi-Mode Microplate Reader* (BioTek Instruments, USA).

The statistics (GraphPad Prism 8.0) included calculation of mean and standarddeviation (M±SD), the percentage of difference between experimental group and control, Mann-Whitney *U* test (control *vs* experimental groups, leaves *vs* roots extracts) and Spearman (r_s) correlation (ethanol concentration *vs* the glutathione system activity in tested samples). The significance level was fixed at $p \leq 0.05$ for all statistical analyses. The Research Ethics Committee of the "Nicolae Testemitanu" State University of Medicine and Pharmacy approved the present study (nr.81 of 19.09.2020).

Results.

The reduced state of glutathione, GSH demonstrated a high variability, in different alcohol extracts of TOL: 10% – 10±0.3 µM/g. Hb, in 20% – 10.9±0.8 µM/g. Hb, in 25% – 12.4±2.2 µM/g. Hb, in 40% – 9.3±1.3 µM/g. Hb, in 50% – 14.6±2.2 µM/g. Hb and in 80% – 18±1.0 µM/g. Hb (Table1). But these amounts where statistically different from control group only in 2 extracts, of 10% and 80%. The GSH recorded a significant, statistically positive correlation (r_s=0.47, p=0.04).

Table 1

Influence of different leaves extracts of TO on glutation content in RBC's

Extracts	GSH (µM/g. Hb)		GSSG (µM/g. Hb)		Total glutathione (µM/g. Hb)	
	Control	TOL	Control	TOL	Control	TOL
LEtOH10	14.72±0.30	9.99±0.27	2.75±0.08	7.75±0.90	17.46±0.22	17.74±1.17
	-32.1% (p=0.05)		+182.1% (p=0.05)		+1.6% (p=0.51)	
LEtOH 20	13.38±5.27	10.88±0.83	3.39±1.99	8.11±0.74	16.77±3.27	18.98±1.57
	-18.7% (p=0.01)		+139.3% (p=0.05)		+13.2% (p=0.28)	
LEtOH 25	8.93±2.01	12.43±2.18	8.84±3.46	9.97±0.09	17.77±1.45	22.40±2.09
	+39.2% (p=0.03)		+12.7% (p=0.51)		+26% (p=0.05)	
LEtOH 40	11.53±1.63	9.26±1.27	7.31±1.24	6.51±1.21	18.84±2.87	15.77±2.48
	-19.7% (p=0.03)		-10.9% (p=0.51)		-16.3% (p=0.13)	
LEtOH 50	9.92±2.71	14.62±2.15	9.16±3.66	8.73±0.64	19.08±0.95	23.35±2.79
	+47.3% (p=0.03)		-4.7% (p=0.83)		+22.4% (p=0.05)	
LEtOH 80	7.78±0.77	18.01±1.02	4.24±0.02	10.39±3.16	12.02±0.78	28.40±2.14
	+131.5% (p=0.05)		+144.9% (p=0.05)		+136.2% (p=0.05)	

Note: LEtOH – leaves extracts in ethanol of different concentration (10-80%).

GSSG was different in TOL ethanolic extracts, as follow: 10% – 7.8±0.9 μM/g. Hb, in 20% – 8.1±0.7 μM/g. Hb, in 25% – 10±0.1 μM/g. Hb, in 40% – 6.5±1.2 μM/g. Hb, in 50% – 8.7±0.6 μM/g. Hb and in 80% – 10.4±3.2 μM/g. Hb. Although the correlation of GSSG tested group *vs* control recorded a light positive value, it didn't reach a statistically significant level (r_s=0.2, p=0.29) (Table 1).

The total amount of GSH in TOL changed as follow: in ethanolic extracts of 10% it was recorded as 17.7±1.2 μM/g. Hb, in 20% – 19±1.6 μM/g. Hb, in 25% – 22.4±2.1 μM/g. Hb, in 40% – 15.8±2.5 μM/g. Hb, in 50% – 23.4±2.8 μM/g. Hb and in 80% – 28.4±2.1 μM/g. Hb (Table 1). The total glutathione recorded a positive, statistically significant correlation to ethanol's concentrations of TOL extracts (r_s=0.45, p=0.05).

The amount of GSH in TOR increased as a result of the action of the bioactive components from the ethanol extracts of 10% (17.74±1.39 μM/g. Hb), 20% (28.03±1.14 μM/g. Hb), 40% (16.48±3.01 μM/g. Hb) and 80% (20.41±0.90 μM/g. Hb) The GSH was decreased under the influence of ethanol extracts of 25% (13.59±0.43 μM/g. Hb) and 50% (13.33±0.69 μM/g. Hb) of TOR extracts. TOR can act as both oxidizing and reducing agents. The GSH recorded a significant, statistically positive correlation (r_s=0.47, p=0.04) (Table 2).

The concentration of GSSG decreased dramatically as a result of the action of the extract on 40% ethanol (2.65±1.30 μM/g. Hb) (Table 2). The GSSG content increased in extracts on ethanol of 20% (5.92±0.72 μM/g. Hb) and 50% (11.46±3.27 μM/g. Hb). In the case of GSSG, the correlation values did not reach the expected statistical threshold (r_s=0.15, p=0.29).

The total glutathione content increased mostly as a result of TOR actions (Table 2). The highest concentrations were determined on alcohol of 10% (28.76±0.54 μM/g. Hb), 20% (33.95±0.42 μM/g. Hb) and 80% (30.93±0.40 μM/g. Hb). The total glutathione content decreased only under the influence of the 25% ethanolic extract of TOR (19.19±0.29 μM/g. Hb). Its content recorded a significant, statistically positive correlation with ethanol concentration (r_s=0.45, p=0.05).

Discussion

Taraxacum officinale is a vigorous plant found worldwide, considered a weed by most gardeners and has been used for many purposes in traditional medicine. This plant is well known demonstrating antioxidant, anti-inflammatory and antitumor properties[15]. The content and effectiveness of TOL and TOR depends of many factors: the period of harvesting, altitudes, soil type, environmental factors (temperature, photoperiod and rainfall) and parts of plant used for extracting. TOL and TOR have different composition due to plants' parts used for experiment. TOL contain a high level of potassium, iron, calcium, magnesium, phosphorus, phenolic compounds and its derivatives (hydroxycinnamic, monocaffeoyltartaric, dicaffeoyltartaric acids); phytosterols (β-sitosterol, stigmasterol, campesterol); vitamins A, B1, B2 and C. TOR are rich in iron, copper and other trace elements; phenolics (chicoric, 4-caffeoylquinic, chloro-

Table 2

Influence of different roots extracts of TO on glutation content in RBC's

Extracts	GSH (μM/g. Hb)		GSSG (μM/g. Hb)		Total glutathione (μM/g. Hb)	
	Control	TOR	Control	TOR	Control	TOR
REtOH10	12.05±0.94	17.74±1.39	8.66±0.70	11.02±1.93	20.71±0.24	28.76±0.54
	+47.2% (p=0.05)		+27.2% (p=0.13)		+38.9% (p=0.05)	
REtOH20	14.15±1.56	28.03±1.14	3.10±0.02	5.92±0.72	17.25±1.54	33.95±0.42
	+98% (p=0.05)		+91.2% (p=0.05)		+96.8% (p=0.05)	
REtOH25	20.81±0.79	13.59±0.43	3.90±0.92	5.60±0.13	24.71±1.71	19.19±0.29
	-34.7% (p=0.05)		+43.5% (p=0.05)		-22.4% (p=0.05)	
REtOH40	8.93±2.01	16.48±3.01	8.84±3.46	2.65±1.30	17.77±1.45	19.13±1.70
	+84.5% (p=0.05)		-70.1% (p=0.05)		+7.6% (p=0.51)	
REtOH50	18.77±3.06	13.33±0.69	3.79±0.71	11.46±3.27	22.57±3.77	24.79±3.96
	-29% (p=0.05)		+202.4% (p=0.05)		+9.9% (p=0.51)	
REtOH80	9.92±2.71	20.41±0.90	9.16±3.66	10.52±0.50	19.08±0.95	30.93±0.40
	+105.7% (p=0.05)		+14.9% (p=0.51)		+62.1% (p=0.05)	

Note: REtOH – roots extracts in ethanol of different concentration (10-80%).

genic, caffeic, p-coumaric, ferulic, p-hydroxybenzoic acids, etc.); sterols (taraxasterol, β-taraxasterol, arnidol, faradiol, α - and β-amyrin, β-sitosterol and stigmasterol); sesquiterpenes (eudesmanolides 4α, 11β, 13,15-tetrahydroridentin B, taraxacolide-O- glucopyranoside, guaianolides 11β,13-dihydrolactucin, etc.) [16–20].

TO represent one of richest vegetable source of beta-carotene and polifenolic compounds as flavonoids and phenolic acids. Many researches are interesting in the distribution of this components in TO, due to high antioxidant activities [10]. Koo *et al.* (2004) were identified in TOL the monocaffeyltartaric, hydroxycinnamic, chicoric, chlorogenic acids; the coumarins, cichorin and aesculin; flavonoids glycosides (luteolin 7-glucoside and two luteolin 7-diglucosides). Luteolin and lutein-7-O-glycoside found in the ethyl acetate fraction of dandelion were reported as to suppress the production of nitric oxide (NO) and prostaglandin E2 in LPS-activated macrophages, which is attributed to suppression of NO and cyclooxigenase-2 (COX-2)- induced synthase, and reduce the level of ROS [21]. Also, it has been reported that this plant act as an anti-inflammatory drug in the central nervous system (CNS), inhibit the production of TNF by blocking IL-1 production in primary cultures of rat astrocytes stimulated with LPSand TNF-alpha-inducing substance[22,23]. These data are confirmed by Jeon*et al.* (2008), which concluded that the aerial parts of *Taraxacum officinale* present anti- angiogenic, anti-inflammatory and anti-nociceptive activities through its inhibition ofNO production and COX-2 expression and/or its antioxidative activity[24]. In one of our previous research we described the action of TO extracts on viability of glial cell line (U-138 MG) assessed by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) test. In that study we reported that TO roots extracts prepared in 80% ethanol had a greater inhibitory action on cells viability than Doxo of 10^5 μg/L [25].

The glutathione and enzymes GPOx, GST, GR are complementary parts of a complex antioxidantsystem developed by the cells, involved in neutralizing H_2O_2 and reduce lipid hydroperoxides [26,27]. Glutathione is a tripeptide with a gamma peptide linkage between the carboxyl group of the glutamate and cysteine. The ratio GSH/GSSG within cells represents a measureof cellular OS. In healthy cells the majority of the total glutathione (90%) is represented by GSH and less than 10% by GSSG. The thiol group of cysteinyl residue of GSH is a source of one reducing equivalent, in thiol protection and redox regulation of cellular thiol proteins under oxidative stress. Fulga *et al.* (2021) demonstrate that TOL and TOR are a valuable source of different classes of biologically active substances, involved in bio- chemical mechanisms, antioxidant protection. TO extracts influence on RBC's thiols level depends of type of extractant and its concentration. The overall influence of TO be to decrease the thiols level, mechanism which depends of their reduced and oxidized forms level in experimental samples, as well of various concentrations and combinations of biologically active substances in different types of extracts [28]. Thus, glutathione is an important naturally occurring antioxidant because it prevents the hydrogen of sulfhydryl group to be abstracted instead of methylene hydrogen of unsaturated lipids. Levels of glutathione are considered of critical importance in tissue injury caused by toxic substances. The combination of antioxidant enzymes and glutathione form offer protection against FR, and there by maintain low levels of lipid peroxide. Park *et al.* (2007) demonstrated that the contents of GPOx, GR and superoxide dismutase (SOD) increased dose dependent manner, and mRNA and protein expression levels of cytochrome P450 2E1 significantly decreased in the dandelion administered group on Sprague-Dawley rats in liver injury induced by carbon tetrachloride (CCl_4) [4]. Another marker of OS is malondialdehyde that was demonstrated by Hagymasi *et al.* (2000), where TOL extract was more effective in membrane protection, (IC_{50}=0.55 mg/ml), compared with the TOR extract (IC_{50}=1 mg/ml). Also, roots and leaves extracts can stimulate the NADPH-cytochrome P-450 reductase activity, the hydrogen-donating ability, reducing power property and radical scavenging capacity of TO. Thehigher hydrogen donor, reducing agent and hydrogen peroxide scavenger capability of the leaf extract correlates with the approximately 3 times higher polyphenol content compared to radix extract [15].

Popovic *et al.* (2001) and Milosevic *et al.*(2003) demonstrated the inhibitory effects of hydroxyl (OH•) radicals production using ethyl acetate, chloroform and water extracts by (flower, leaf, stem and root) of TO which exerts antioxidant activity [29].

Wojdylo *et al.* (2007) demonstrated the high scavenging activity of DPPH radical was in TOR of 80 % methanol extract, but other researches described the low activity in ABTS and FRAP assays using the same TOR methanolic extracts [30].

Sumanth M. and Rana A.C. (2006)demonstrated that pretreatment of Wistar albino rats with 100 mg/kg *per os* ofTO extract improved significantly the SOD, CAT, GSH and GPOx levels and reduced lipid peroxidation [29].

Conclusions.

Taraxacum officinale exhibits a strong antioxidant activity. This plant has ability to prevent and treat the damage of cells caused by oxidative stress process, by actioning on glutathione system. This activity depends of ethanol concentrations and plant's part.

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Conflict of interests.

The authors declare that there is no conflict of interests regarding the publication of this paper.

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