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Evaluation of the Toxicity of a New Series of ά-Aminophosphonate Derivatives in Non-Target Population (*Triticum Durum* Desf)

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KEYWORDS

Green chemistry; ά-aminophosphonate; *Triticum durum*, stress biomarkers; green pesticides.

ABSTRACT:

Introduction: α-Aminophosphonates play an important role across several fields, including organic synthesis and various potential applications.**Objectives**: Lacinia at quis risus sed vulputate odio ut enim. Orci porta non pulvinar neque laoreet suspendisse interdum. Consequat mauris nunc congue nisi vitae suscipit. Morbi quis commodo odio aenean.

Methods: Using an immersion ultrasound-assisted method, a new series of ά-aminophosphonate derivatives (BR1, BR2, BR3, BR4, and BR5) was tested for toxicity in a non-target population (*Triticum durum* Desf). For this, we monitored certain stress biomarkers, namely glutathione (GSH), glutathione-s-transferase (GST) and catalase (CAT) compared to the reference pesticide (Dursban).

Results: The results obtained show a significant increase in GSH for BR1, BR4 and BR5, an induction of GST activity for all treatments and of catalase activity for high concentrations of BR1, BR2 and BR3 molecules.

Conclusions: Thanks to the addition of the pharmacophore fragment, the five α-aminophosphonate molecules can be used as a green pesticide since they have a non-significant impact on the non-target population (*Triticum durum* Desf), even the few disturbances observed in wheat will be dissipated over time due to its ability to tolerate these stressful conditions.

1. Introduction

Since the 1940s, pesticides or phytosanitary products have been applied preventively in order to repel or mitigate the effects of harmful organisms [1]. They have become omnipresent in the earth, their development has contributed to improving our quality of life. Twenty years later, the use of these phytosanitary products around the world has increased alarmingly [2] and their use almost doubled between 1990 and 2018, from 1.7 to 2.7 million tons* [3], given the consequences of the demographic growth of the world population which increased from 2.5 billion in 1950 to more than 8 billion in 2022 according to the official United Nations estimate. Among the procedures already launched by the European Commission is to harmonize the rules in terms of authorized and prohibited pesticides, and maximum thresholds of residues present in order to reduce their use 50% and therefore their impact on health and the environment, but also promote to use alternative products or techniques.

A new discipline of green chemistry inspired by the concept of sustainable development has been formulated since the 1990s, in order to design chemical products and processes to reduce or eliminate the use and synthesis of dangerous substances. Among these products, organophosphate compounds of the phosphonate type which are analogues of natural phosphates which cover a wide field of application due to their different chemical and biological properties as

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well as their flexible structures and rich in heteroatoms [4, 5]. In these compounds the P-O bond is replaced by a P-C bond, this substitution provides access to compounds capable of resisting enzymatic hydrolysis [6].

Furthermore, the different substances that make up pesticides directly target the pests of durum wheat: weeds, fungi and insects. Durum wheat is part of the cereal family, it occupies first place in world production and second in the daily diet of the population [7] durum wheat becomes the intangible cultural heritage of humanity and cultivated on nearly 17 million hectares worldwide [8]. In Algeria, the cultivation of durum wheat constitutes a strategic crop in the economic development plan [9] and it is considered a predominant activity in agriculture. The permanent use of these phytosanitary products and changes in agricultural practices regarding the use of pesticides can cause harmful effects on the plant, capable of modifying their metabolism and their morphology, which alters their growth and development by causing an overproduction of ROS that generate oxidative stress and consequently a reduction in productivity and quantitative and qualitative losses in yields [10].

For this, particular attention was paid to the synthesis of new α-aminophosphonate derivatives which constitute a specific family of phosphonates [11, 12], new synthesis route towards derivatives biological in soft and green conditions, due to their biological activities [13,14]. They are known as amino acid analogues [15], which is why α-aminophosphonates compete with their amino acid analogues to access the active centers of enzymes or other cellular targets. Several activities are known for the latter, including those which interest us the most, in relation to our study, their antifungal [16] and herbicidal [17] activities. In addition, phosphonates have a chelating property which gives them a strong affinity for the mineral part of the soil. Their mobility is very low [18], which means that the risk of groundwater contamination is reduced. They are also degradable by certain bacteria which have developed the capacity to metabolize phosphonates as nutrient sources [19].

In Algeria, the use of pesticides for agricultural use is increasingly frequent, following the increase in cultivated areas and the diversity of crop pests. Thus, nearly 400 active pesticide substances, including around 7,000 specialties, are marketed annually under the term “plant protection products for agricultural use” [20]. According to the Food and Agriculture Organization of the United Nations, Algerian consumption of phytosanitary products in kilograms per hectare is estimated at nearly 22.32 in 2016.

2. Objectives

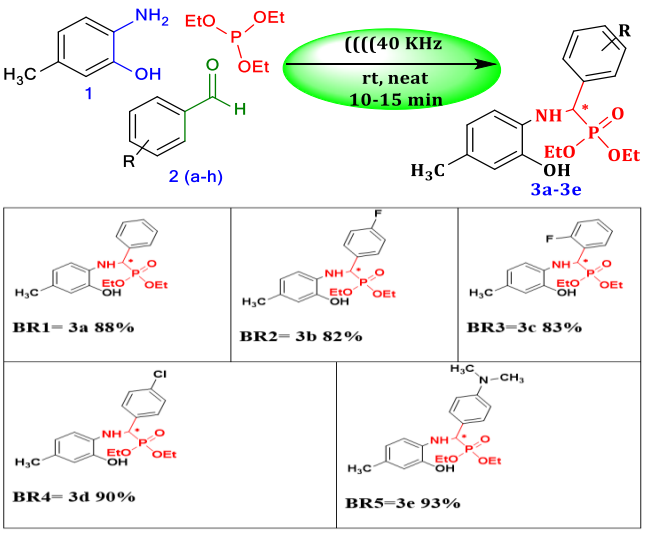
In this context that our work was carried out to evaluate the toxic potential of a series of newly synthesized α-aminophosphonate derivatives, by a new rapid and practical approach, based on the one-pot reaction of the 2 -hydroxyaniline, aromatic aldehydes and triethyl phosphite, on a non-target population (*Triticum durum* Desf).

3. Methods

2.1. Chemical material

2.1.1. Synthesis of α-aminophosphonates

A new series of α-aminophosphonates was synthesized using ultrasound irradiation, beginning with 2-hydroxyaniline, aromatic aldehydes, and triethylphosphite (Scheme 1). The yields were relatively high, ranging from 82% to 93%. All compounds’ structures have been determined using appropriate spectroscopic methods such as NMR ^{1}H, ^{13}C, ^{31}P, MS and IR. The synthesis was described by Bahadi et al. (2022) [14].



Scheme 1. Synthesis of α-aminophosphonates 3a-3e.

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2.1.2. Solution preparation

Separately, the five α-aminophosphonate molecules (BR1, BR2, BR3, BR4, and BR5) were dissolved in 100 ml of distilled water containing 10% DMSO (90 ml/10 ml). DMSO was chosen because of its rapid evaporation and lack of residual effect. The wheat treatment was carried out by spraying these aminophosphonates according to the concentrations indicated in the following table (01)

2.2. Biological material

Our choice fell on durum wheat (*Triticum durum* Desf) supplied by Moulins Amor BENAMOR. Wheat treatment has carried out by spraying aminophosphonates at concentrations indicated in the following table:

Table 1: The concentrations of the five α-aminophosphonate derivatives used in durum wheat.

Molecules	Concentrations (µmol/l)	
BR1	**400**	**440**
BR2	**400**	**440**
BR3	**340**	**500**
BR4	**340**	**500**
BR5	**340**	**500**

2.3. Experimental protocol

The sowing of durum wheat seeds, previously disinfected with a 3+ sodium hypochlorite solution for 5 minutes then rinsed with distilled water, was carried out in plastic pots, filled with a mixture composed of potting soil of increasing quantity, and gravel of decreasing quantity. Watering of 150 ml per pot was carried out 3 times per week (distilled water, a nutrient solution for the controls and solutions prepared for the treated). For each concentration three repetitions were performed.

2.4. Analysis techniques

2.4.1. Determination of GSH level

The GSH level is determined using the method of Weckberker and Cory (1988) [21]. The principle of this method is based on the colorimetric measurement of 2-nitro 5-mercapturic acid, resulting from the reduction of 5-5'-dithio-bis-2-nitrobenzoic acid (DTNB) by the thiol group (- SH) of glutathione. The absorbances were read at a wavelength of 412 nm. The results are expressed in µmol/mg of protein. Glutathione (GSH) level was estimated as follows:

$$\boldsymbol{GSH\ (umol/mg\ of\ protein)} = \frac{\boldsymbol{OD \times VT \times Vt}}{\boldsymbol{e \times Vh \times vs \times mg\ of\ protein}}$$

where, OD is the difference in optical density obtained after hydrolysis of the substrate; VT is the total volume of the solutions used in the deproteinization - 1 (0.2 ml ASS+ 0.8ml homogenate); Vt is the total volume of solutions used in the assay - 1.525 (0.5 ml supernatant + 1 ml tris/EDTA + 0.025 ml DTNB); e is 13.1, the molar extinction coefficient for the thiol group (-SH); Vh is the volume in ml of the homogenate used in the deproteinization (0.8); Vs is the volume in ml of supernatant used 0.5; mg of protein is the quantity of protein expressed in mg..

2.4.2. Determination of Catalase (CAT) activity

Preparation of the enzymatic extract: The root and leaf samples (1 g of fresh material) are homogenized in phosphate buffer (50 mM phosphate, pH = 7.8) in an ice bath. The homogenate is then filtered using a suitable cloth before carrying out a cold centrifugation at 12,000 g for 15 min (Sigma 3-16 k centrifuge), the supernatant is stored at 4°C and used for the enzymatic assays (CAT and GST)

Catalase activity is determined according to (Cakmak & Horst, 1991) [22]. For a final volume of 3 ml, the reaction mixture contains 100 µl of the crude enzyme extract, 50 µl of 0.3% hydrogen peroxide H2O2 and 2.8 ml of NaK buffer (50 mM Na K, pH= 7 ,2). The decomposition rate of H2O2 is determined by measuring the decrease in absorbance at 240 nm for one minute; the device is calibrated in the absence of the enzymatic extract. Catalase activity is expressed in nmol/min/mg of protein (Σ =39.4M-1 cm-1L).

2.4.3. Measurement of Glutathione S-Transferase (GST) activity

The measurement of Glutathione-S-Transferase is determined by the method of Habig et al 1974[23]. It is

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based on the conjugation reaction between GST and a substrate, CDNB in the presence of Glutathione (GSH), the reading of the absorbances is recorded every 15 seconds for 1 minute at 340 nm in a visible/UV spectrophotometer against a blank containing 200 µl of distilled water replacing the quantity of supernatant. GST activity is expressed in nmol/min/mg of prot.

2.4.4. Quantification of spectrophotometric measurements

The following formula is used in the quantification of the different spectrophotometric measurements following the enzymatic assays of CAT and GST [24].

$$Act = (\Delta A.V\_t)/(\varepsilon\ \Delta t.L.V\_e.p)$$

Act: Enzymatic activity in nmole/min/mg of Protein.

ε: Molar linear extinction coefficient in M.

ΔA: Average difference in absorbance.

Vt: Total volume of the reaction mixture in m

4. Results

3.1. Effect of α-aminophosphonates on Glutathione (GSH) levels

The figure illustrates the variations in the level of glutathione GSH in durum wheat treated with different concentrations of α-aminophosphonates, reference pesticide and the control.

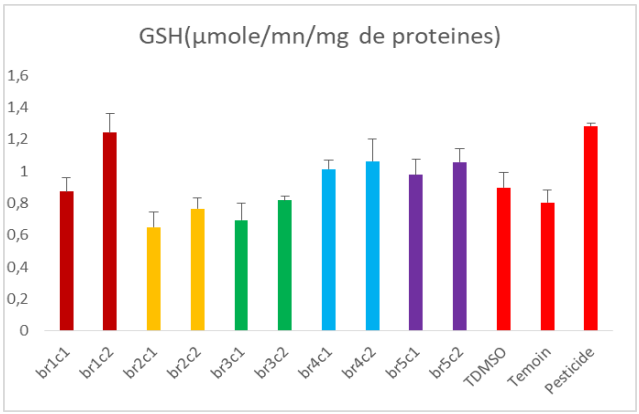

Figure 1: Effects of five α-aminophosphonates molecules (BR1, BR2, BR3, BR4, BR5)

on the GSH level of durum wheat

We note from the figure 1 that the GSH level increases in wheat treated with different concentrations of BR1, BR4 and BR5 molecules while it decreases for BR2 and BR3 molecules compared to the control after 7 days of treatment.

All the values recorded remain lower than the value of the pesticide which reaches a maximum equivalent to 1.28 umol/min/mg of proteins, an increase of 37% compared to the control. Note also that the BR1C2 concentration has a GSH level almost identical to that of the reference pesticide.

3.2. Effects of α-aminophosphonates on Catalase (CAT) activity

The effect of the five α-aminophosphonate molecules on catalase activity in treated wheat compared to the control is illustrated in Figure 2

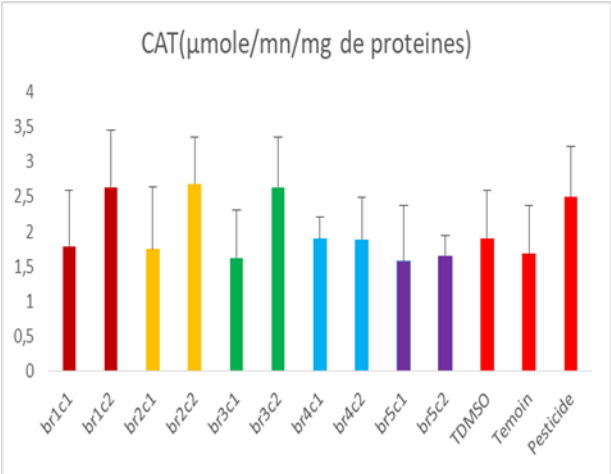

Figure 2 : Effects of five α-aminophosphonates molecules (BR1,BR2, BR3, BR4, BR5)

on the CAT activity of durum wheat

Our results show that wheat treated with low concentrations of the molecules BR1 and BR2 and BR3 as well as the different concentrations of the molecules, BR5, show no induction of CAT activity compared to the control after 7 days of exposure.

On the other hand, we note a significant increase equivalent to 30% in catalase activity in wheat treated with high concentrations of the same molecules (BR1, BR2, BR3) compared to the control value and which is

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similar to that of the reference pesticide at the end of treatment.

3.3. Effects of α-aminophosphonates on glutathione S-transferase (GST) activity

According to Figure 3 which presents the effect of increasing concentrations of α-aminophosphonate molecules on GST activity in wheat after 7 days of treatment, we note a significant increase in this activity for all treatments compared to that of the witness. The highest value is recorded respectively for the BR3C1 and BR3C2 molecules (0.056 and 0.060 µmole/min/mg of proteins) which largely exceeds the GST activity induced by the presence of the pesticide (0.045 µmole/min/mg of proteins).

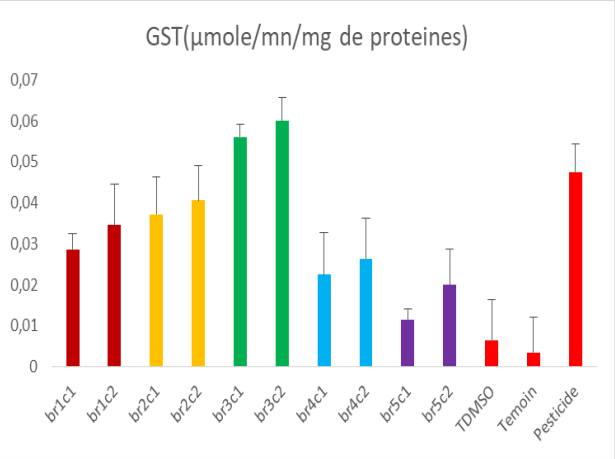

Figure 3: Effects of five α-aminophosphonates molecules (BR1,BR2, BR3, BR4, BR5) on the GST activity of durum wheat

5. Discussion

The plant exposed to different types of stress implements various defense strategies, constitutive or induced. It perceives a stimulus which causes the emission of signals. The latter are transmitted inside the plant cell by triggering the activation of genes coding for metabolic enzymes in order to synthesize defense molecules such as catalase and superoxide dismuta. [25, 26,27, 28] as well as the strengthening of the non-enzymatic defense system to deal with the generation of ROS [29].

In the present study, we were interested in evaluating non-enzymatic antioxidants such as glutathione as well as the variation in the level of enzymatic antioxidants such as Glutathione S-transferase and catalase in durum wheat. Glutathione is a major antioxidant in plant cells, the most abundant and involved in the protection of cells against the toxic effects of xenobiotics [30]. This tri-peptide plays many physiological roles in plants, it is involved in different processes such as cell differentiation [31], resistance to pathogens [32], maintenance of redox balance in cellular compartments thanks to its oxidized form (GSSG). [33]. It is also involved in anti-radical defense through its involvement in detoxification reactions catalyzed by GST. [34].

According to our results, a significant increase in GSH levels was observed in wheat leaves treated with BR1, BR4, BR5 and Dursban. Several authors have explained that GSH in the reduced state reflects the antioxidant competence of cells [35], it is linked to different forms of stress and its accumulation is often concomitant with that of ROS [36]. Indeed, ROS are involved in the signaling cascades responsible for the induction and regulation of numerous defense genes including that of GSH [37]. It should be noted that all of the GSH values remain lower than the values of the reference pesticide with the exception of the high concentration of BR1 (C2BR1) which presents a level almost identical to that of Dursban showing that this molecule induces a burst oxidative due to its high toxicity compared to other molecules.

The same goes for the induction of GST, which explains its involvement in the transport and elimination of reactive compounds performing other antioxidant functions such as catalase, glutathione and superoxide dismutase [38,39]. Indeed, Glutathione S-transferase forms a superfamily of multifunctional enzymes such as peroxidase, isomerase or thiol transferase activity, thus involved in the modulation of cell signaling [40]. It is very soluble and considered a major enzyme in the enzymatic detoxification of xenobiotics, involved in the response of plants to different biotic and abiotic stresses [41].

Indeed, GST is a multifunctional phase II enzyme which plays an essential role in the conjugation of electrophilic compounds (phase I metabolites) and catalyzes the conjugation of GSH with substances of an endogenous or exogenous nature. The increase in GST activity indicates both a high concentration of

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xenobiotics present in the environment and the induction of oxidative stress following the increasing production of ROS [42]. In the present study, we found a dose-dependent increase in GST activity in wheat leaves treated with all five α-aminophosphonate molecules and Dursban compared to the control at the end of treatment. These results are in agreement with those of Belaid and Sbartai (2021) [43] who link its increase to its intervention in the conjugation of glutathione-pesticide during phase II of metabolism. The work of Bouchlaghem (2011) [44] demonstrated a significant increase in the GST rate in durum wheat Tritucum durum exposed to phosphate fertilizers (NPK) in the stems after seven days of treatment. Also, the work of Sbartai (2012) [45]determined that the induction of GST activity in tomatoes exposed to cadmium allows the plant to tolerate and then adapt to this xenobiotic. Additionally, Vranova et al. (2002) [46] showed that low doses of the xenobiotic allow the establishment of antioxidant enzymes and the arrest of the cell cycle while high doses of ROS cause cell death. In our case, all of our results indicate that all molecules induce low to moderate oxidative stress in the non-target population, attenuated by the intervention of the antioxidant system.

At the same time, we recorded the induction of CAT activity with the different treatments, which demonstrates the installation of oxidative stress. CAT is an important enzyme in the defense system and considered a central biomarker in protection against oxidative stress [47]. It catalyzes, extremely quickly, the disproportionation of oxygen peroxide (H2O2) in to oxygen and water [48], thus protecting cells from oxidative effects. The change in CAT activity is explained by cellular damage caused by exposure to contaminants [49]. In our experiment, we noted that wheat treated with high concentrations of BR1, BR2 and BR3 molecules undergo a significant induction of CAT activity compared to the control during the exposure period and which appears almost identical to that of Dursban. Our results are in agreement with those obtained by Ferfar et al. (2016) [50] who demonstrated an increase in CAT activity in two varieties of wheat (Simeto and Cirta) exposed to two sulfonylurea herbicides, in the leaves and roots of wheat “Triticum aestivum L”. Likewise, the results of Belahcene et al. (2015) [51] which highlight the influence of oxidative stress caused by a systemic herbicide Cossack on the CAT activity of three varieties of durum wheat (Sersou, Carioca and Wersenis) where a very significant genotypic variability was noted resulting from the response of each variety with respect to the applied stress. Kim et al. (2005) [47] and Khosravinejad et al. (2008) [52] showed that CAT activity increases in cereal leaves during stress and it is higher in plants exposed to several stress situations in order to protect them against adversity and ensure their survival [53, 54, 55, 56, 57]. Also, the work of Benhamadi ASMA 2014 [61] revealed an increase in CAT activity with the concentration of metalloids (Antimony Sb; Arsenic As) in the upper parts of the plant. Indeed, the increase in this activity can be explained by the toxicity of the molecules which affected the functioning of the plant, which caused the triggering of detoxification systems through the synthesis of CAT. This allows the plant to survive the stress caused by these molecules and to eliminate ROS.

Organophosphates are valued for their ease of production, higher toxicity to insects and biodegradability, which ensures low persistence in the environment. The green synthesis of aminophosphonate derivatives is an alternative solution to the use of aminophosphonates, which are less chemically and metabolically stable than their derivatives. According to our results, the three molecules BR1, BR2 and BR3 seem to be more toxic compared to BR4, BR5 but their toxicity is attenuated by the defense system represented in our case by GSH, GST and CAT. Thanks to the addition of the pharmacophore fragment, the five α-aminophosphonate molecules can be used as a green pesticide since they have a non-significant impact on the non-target population (Triticum durum desf), even the few disturbances observed in wheat will be dissipated over time due to its ability to tolerate these stressful conditions.

Refrences

[1] Ayad Mokhtari N., Identification And Dosage Of Pesticides In Agriculture And Related Environmental Problems (Online), Magister's Diploma, Faculty of Organic Chemistry, University of Oran, Algeria, 2012. 13p.

[2] Haarstad K., John Bavor J., Roseth R.., 2012. The Open Environmental & Biological Monitoring.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 680-688 | ISSN:2251-6727

Pesticides in Greenhouse Runoff, Soil and Plants A Screening. 5, 1-13.

[3] FAO. Pesticides use. available at https://www.fao.org/faostat/en/#data/RP/visualize. 2020.

[4] Nowack B., 1998. The behavior of phosphonates in wastewater treatment plants of Switzerland. Water Research. 32(4), 1271–1279. https://doi.org/10.1016/S0043-1354(97)00338-2

[5] Salasi M., Shahrabi T., Roayaei E., Alifkhazraei M., 2007. The electrochemical behaviour of environment-friendly inhibitors of silicate and phosphonate in corrosion control of carbon steel in soft water media. Mater Chem Phys. 104 (1), 183–190. https://doi.org/10.1016/j.matchemphys.2007.03.008

[6] Francis MD., Russell RG., Fleisch H.,1969. Diphosphonates Inhibit Formation of Calcium Phosphate Crystals in vitro and Pathological Calcification in vivo. Science. 165 (3899), 1264-1266. https://doi.org/10.1126/science.165.3899.1264

[7] Slama A., Ben Salem M., Zid E., 2005. Cereals in Tunisia: production, effect of drought and resistance mechanisms. Science and global change/Drought. 16(3), 225- 229.

[8] Abecassis J., Allaoua A., Ben Becher L., Elloumi M., Gharbi S., 2017. Durum wheat: from the organization of sectors to the structuring of a Mediterranean network. IPEMED Palimpsestes hal-02788748. 18, 15.

[9] Djermoun A., Cereal production in Algeria: the main characteristics, Department of Agronomy, University of Hassiba Benbouali of Chlef, 2009.

[10] Fritas S., Bioecological study of the complex of insects linked to cereal crops in the Batna region. (Algeria), Master's thesis, Option : Ecology and population biology, Abou Bakr Belkaid University. Tlemcen, Algeria. 2012, 115p.

[11] Saib A., Berrebbah H., Berredjem M., Djebar M.R., 2014. Cytotoxic study of three derivatives amidophosphonates on alternative cellular model : Paramecium tetraurelia. toxicology research. 3(5), 395-399.

[12] Rachedi K.O., Ouk T.S., Bahadi R., Bouzina A., Djouad S.E., Bechlem K., 2020. Synthesis, DFT and POM analyses of cytotoxicity activity of α-amidophosphonates derivatives: Identification of potential antiviral O, O-pharmacophore site. Journal of Molecular Structure. 1197, 196-203. https://doi.org/10.1016/j.molstruc.2019.07.053

[13] Aissa R., Guezane-Lakoud S., Gali L., Toffano M., Ignaczak A., Adamiak M., Merabet-Khelassi M., Guillot R., Aribi-Zouioueche L., 2022. New promising generation of phosphates α-aminophosphonates: Design, synthesis, in-vitro biological evaluation and computational study. Journal of Molecular Structure. 1247 (17), 131336.

[14] Bahadi R., Boughoula R., Berredjem M., Bachari Kh., Bouzina A., Bouacida S., Sbartai H., Benalliouche F., Redjemia R. 2022. A convenient synthesis, biological activity and X-ray crystallography of novel α-aminophosphonate derivatives. Phosphorus, Sulfur, and Silicon and the Related Elements. 197(11), 1150-1156. https://doi.org/10.1080/10426507.2022.2064859

[15] Benbouguerra Kh., Chafaa S., Chafai N., Mehri M., Moumeni O., Hellal A., 2018. Synthesis, spectroscopic characterization and a comparative study of the corrosion inhibitive efficiency of an a-aminophosphonate and Schiff base derivatives: Experimental and theoretical investigations. Journal of Molecular Structure. 1157,165-176. https://doi.org/10.1016/j.molstruc.2017.12.049

[16] Hellal A., Chafaa S., Chafai N., 2015. Synthesis, antibacterial and antifungal screening of three new of alpha-aminophosphonic acids. International Journal of Scientific & Engineering Research. 6(8), 1622 – 1627.

[17] Allen M.C., Fuhrer W., Tuck B., Wade R., Wood J. 1989. Renin inhibitors. Synthesis of transition-state analog inhibitors containing phosphorus acid derivatives at the scissile bond. Medicinal chemistry journal. 32, 1652. https://doi.org/10.1021/jm00127a041

[18] Kuliszewska E., Hanbauer M., Hammerschmidt F.,2008. Preparation of α-Aminobenzylphosphonic Acids with a Stereogenic Quaternary Carbon Atom via Microscopically Configurationally Stable α-Aminobenzyllithiums. - Chemistry : A European Journal. 14(28), 8603-8614.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 680-688 | ISSN:2251-6727

[19] Huang J., Su Z., Xu Y., 2006. The evolution of microbial phosphonate degradative pathways. Journal of Molecular Evolution. 61 (5), 682–90.

[20] Bouziani M. Immoderate use of pesticides : Serious health consequences. The guide to medicine and health, Santémaghreb, 2007.

[21] Weckberker G., Cory J.G., 1988. Ribonucleotide reductase activity and growth of glutathione-depleted mouse leukemia L1210 cells in vitro. Cancer Letters. 40 (1988), 257-264.

[22]Cakmak I., Horst J.H., 1991. Effects of Aluminium on Lipid Peroxidation, Superoxide Dismutase, Catalase, and Peroxidase Activities in Root Tips of Soybean (Glycine Max). Physiologia Plantarum .83,463-468. http://dx.doi.org/10.1111/j.13993054.1991.tb00121.x

[23] Habig W.H., Pabst M.J., Jakoby W.B. 1974. Glutathione S-transferases The first enzymatic step in mercapturic acid formation. The Journal of Biological Chemistry. 249 (22), 7130-7139.

[24] Servais S. Mitochondrial alterations and pulmonary oxidative stress in response to ozone: effects of age and Omega-3 supplementation . Claude Bernard-Lyon 1 University, 2004. 19-35p.

[25] Kangasjärvi J., Talvinen J., Utriainen M., et al., 1994. Plant defence systems induced by ozone. Plant Cell Environ. 17, 783–794.

[26] Pell E.J., Schlagnhaufer C.D., Arteca R.N. 1997. Ozone-induced oxidative stress : mechanisms of action and reaction. Physiol Plant. 100, 264–273.

[27] Noctor G., Foyer C.H., 1998. Ascorbate and glutathione : keep-ing active oxygen under control. Annual Review of Plant Phys-iology and Plant Molecular Biology. 49, 249–279.

[28] Yaiche F., sbartai H., Sbartai I., Meksem L., Ouali kh., 2017. Cellular réponses observed following contamination by the pathogen of task halo " pyrenophoratrirtici-repentis" or heavy métal " copper" in durum wheat (tritium durum desf). Int.J. PHarm.Sci.Rev.Res. 44(2), 136-144.

[29] Hasanuzzaman M., Bhuyan M.B , Raza A., Hawrylak-Nowak B., Matraszek-Gawron R., Mahmud J.A., et al. 2020. Selenium in plants : Boon or bane Environ. Exp. Bot. 178, 104170. doi: 10.1016/j.envexpbot.2020.104170

[30] Dickinson D.A., Forman H.J., 2002. Cellular Glutathione and Thiols Metabolism. Biochemical Pharmacology.64,1019-1026. https://doi.org/10.1016/S0006-2952(02)01172-3

[31] Ogawa H., et al., 2004. Allergic bronchopulmonary fungal disease caused by Saccharomyces cerevisiae. J Asthma. 41(2), 223-8.

[32] Foyer C.H., Noctor G., 2005. Redox Homeostasis and Antioxidant Signaling: A Metabolic Interface between Stress Perception and Physiological Responses. Plant Cell. 17, 1866-1875. http://dx.doi.org/10.1105/tpc.105.033589

[33] Foyer C.H and Noctor G., 2003. Redox sensing and signalling associated with reactive oxygen in chloroplasts, peroxisomes and mitochondria. Physiologia Plantarum. 119, 355-364.

[34] Barillet S. toxicokinetics, chemical and radiological toxicity of uranium in zebrafish (daniorerio). Doctoral thesis in environmental toxicology, University of Metz, France, 2007, 326p.

[35] Akerboom T., Sies H., Glutathione transport and its significance in oxidative stress. In Glutathione (1990). CRC Press, 2017, 45-56p.

[36] Benavides M.P., Gallego S.M., Tomaro M.L., 2005. Cadmium toxicity in plants. Braz. J. Plant Physiol. 17, 21-34.

[37] Wang et al., 2003. Asian-Aust. J. Anim. Sci. 16 (10), 1487-1494.

[38] Sies H., 1993. Strategies of Antioxidant Defense. European Journal of Biochemistry. 215, 213-219. http://dx.doi.org/10.1111/j.1432-1033.1993.tb18025.x

[39] Livingstone D.R., 2003. Oxidative stress in aquatic organisms in relation to pollution and aquaculture. Revue de Medicine Veterinaire. 154, 427-430.

[40] Dixon J., Durrheim K., Tredoux C., Tropp L.R., Clack B., Eaton E., 2010. A paradox of integration?Interracial contact, prejudice reduction and black South Africans' perceptions of racial discrimination.Journal of Social Issues. 66, 403-418.

[41] Anjum N.A., Umar S., Ahmad A., Oxidative stress in plants: causes, consequences and tolerance. IK International Publishing House : New Delhi, 2012

[42] Bhagat K.K., Chang C.N., Chang C.Y., 2016. The Impact of the Flipped Classroom on Mathematics

Journal of Chemical Health Risks

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JCHR (2024) 14(2), 680-688 | ISSN:2251-6727

Concept Learning inHigh School. Educational Technology & Society. 19 (3), 124–132.

[43] Belaid Ch., Sbartai I., 2021. Assessing the effects of Thiram to oxidative stress responses in a freshwater bioindicator cladoceran (Daphnia magna). Chemosphere. 268, 128808.

[44] Bouchelaghem S., Djebar Berrebbah H., Djebar M.R., 2011. The impact of dust emits by the steel complex of El Hadjar (ANNABA) on two biological models : Mousses and lichens. African Journal of Biotechnology. 10(18), 3574-3578.

[45] Sbartai H., Djebar M.R., Sbartai I., Berrabbah H., 2012. Bioaccumulation of cadmium and zinc in tomato (Lycopersicon esculentum L.). Comptes Rendus Biologies. 335 (9), 585-593.

[46] Vranová E., Inzé D., Van Breusegem F., 2002. Signal transduction during oxidative stress. J Exp Bot. 53, 1227–1236.

[47] Kim J.C., Simmins P.H., Mullan B.P., Pluske J.R., 2005. The digestible energy value of wheat for pigs, with special reference to the post-weaned animal [Review]. Anim. Feed Sci. Technol. 122 (34), 257-287.

[48] Bhaduri A.M., Fulekar M.H., 2012. Assessment of arbuscular mycorrhizal fungi on the phytoremediation potential of *Ipomoea aquatica* on cadmium uptake. *3 Biotech.* 2, 193–19.

[49] Shijin W., Ermiao W., Lequan Q., Weihong Z., Jianmeng C., 2011. Effects of phenanthrene on the mortality, growth, and anti-oxidant system of earthworms (Eisenia fetida) under laboratory conditions. Chemosphere. 83, 429-434.

[50] Ferfar .M, Meksem Amara L., Grara N., Meksem N., Bensaid M., Djebar M.R. 2016. Phytotoxic Effects Of A Sulfonylurea Herbicide On Two Varieties Of Durum Wheat (Triticum Durumdesf). International Journal Of Pharmaceutical Research & Kiallied Sciences. 5(4), 159-168.

[51] Bellahcene Z., Bouhamida M., Mokhtari A., 2015. Fuzzy sliding mode control with pi based on genetic algorithm optimization for unmanned aerial quadrotor vehicle. In International Conference on Automation and Mechatronics. USTO Oran. 3 (64), 77- 115.

[52] Khosravinejad F., Heydari R., Farboodnia T., 2008. Effects of Salinity on Photosynthetic Pigments, Respiration, and Water Content in Two Barley Varieties. Pakistan Journal of Biological SciencesYear.11(20),2438-2442. https://doi.org/10.3923/pjbs.2008.2438.2442

[53] Nepomuceno L.A., 2001. Tolerância à seca em plantas. Biotecnologia ciênciae desenvolvimento.2, 12-18.

[54] Taiz L., Zeiger E., Plant Physiology (Third Edition). Sinauer Associates, Inc., Publishers : Sunderland, 2002. pp 67-86.

[55] Pang B.o., Lillian L., Shivakumar V., 2002. EMNLP '02: Proceedings of the ACL-02 conference on Empirical methods in natural languageprocessing.10,79-86. https://doi.org/10.3115/1118693.1118704

[56] Reddy V., Urooj A., Kumar A., 2005. Evaluation of antioxidant activity of some plant extracts and their application in biscuits. Food Chemistry. 90 (1), 317-321.

[57] Mishra S., Srivastava S., Tripathi R.D., Govindarajan R., Kuriakose S.V., Prasad M.N., 2006. Phytochelatin synthesis and response of antioxidants during cadmium stress in Bacopa monnieri L. b Plant Physiology and Biochemistry. 44(1), 25-37.

[58] Benhamdi A., Bentellis A., Oualida Rached O., Du Laing G., Mechakra A., 2014. Effects of Antimony and Arsenic on Antioxidant EnzymeActivities of Two Steppic Plant Species in an Old AntimonyMining Area. Biol Trace Elem Res. Apr ; 158(1):96-104.