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Chemo-Informatic Comparison of Gibberellins and Anti-Gibberellins

Ivan Andújar*, Daviel Gómez, Lianny Pérez and José Carlos Lorenzo

Bioplant Center, University of Ciego de Avila, Ciego de Ávila, 69450, Cuba.

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ABSTRACT

Molecular descriptors to differentiate four gibberellins and seven anti-gibberellins were studied. DRAGON software and Cambridge Soft ChemOffice were used to calculate 212 descriptors. Of them, 48 showed statistically significant differences between gibberellins and anti-gibberellins which can be summarized as follows. Gibberellins contain as average 14.3 times more 7-membered rings, 14.3 times more 9-membered rings, 7.4 times more ring tertiary carbon (sp3), 6.1 times more terminal tertiary carbon (sp^3) and 6.0 times more terminal quaternary carbon (sp^3) than anti-gibberellins. Also gibberellins usually have ring quaternary carbon (sp^3) and aliphatic secondary carbon (sp^2) while anti-gibberellins usually do not. On the other hand, anti-gibberellins generally have aromatic ratio, aromatic bonds, nitrogen atoms, chlorine atoms, halogen atoms, benzene-like rings, aromatic carbon (sp^2), unsubstituted benzene carbon (sp^2) and substituted benzene carbon (sp^2) while gibberellins usually do not. A dendrogram was obtained after conducting a hierarchical cluster analysis with data of chemical molecular descriptors with statistical significant differences (48). The dendrogram correctly classified gibberellins and anti-gibberellins in two independent branches.

Keywords: Chemo-informatics, Molecular descriptors, Plant growth regulators

INTRODUCTION

Gibberellins are among the most important substances for regulating growth and morphogenesis in plant cell, tissue and organ culture [1,2]. They have been used, for instance, to control in vitro morphogenesis of sugarcane [3] pineapple [4], potato [5] bromeliads [6,7]. Modification of gibberellic acid levels are able to alter the biomass production, its allocation and may affect chemical resistance, but not tolerance [8]. The applications with gibberellic acid and abscisic acid to grapevines cv. Malbec may improve the transport of photo-assimilates from leaves to fruits by up-regulation of sugar transporters at different phenological stages [9].

On the other hand, a wide range of synthetic substances, often called ¨anti-gibberellins¨, acts by blocking biosynthesis pathways. These were in general developed to achieve desirable agricultural outcomes, such as dwarfing. Anti-gibberellins are classified into four categories [10]. A number of quaternary ammonium, phosphonium and sulphonium salts act by inhibiting the cyclization process. An example of this type is chlormequat chloride (CCC), very used to regulate tomato growth and yield [11]. Certain heterocyclic nitrogen-containing compounds such as ancymidol, paclobutrazol, uniconazole-P and tetcyclacis appear to act by inhibiting ent-kaurene oxidase [12] A further group of inhibitors are acyl cyclohexanedione derivate, for example prohexadione and diaminozide, which affect the later steps of gibberellin biosynthesis involving hydroxylases [13].

Agricultural effects of gibberellins and anti-gibberellins have been widely documented but their chemical contrasts need more studies. The present study compared the molecular descriptors of four gibberellins and seven anti-gibberellins **(Figure 1)**.

Corresponding author: Jose Carlos Lorenzo, Bioplant Center, University of Ciego de Avila, Ciego de Ávila, 69450, Cuba, E-mail: jclorenzo@bioplantas.cu

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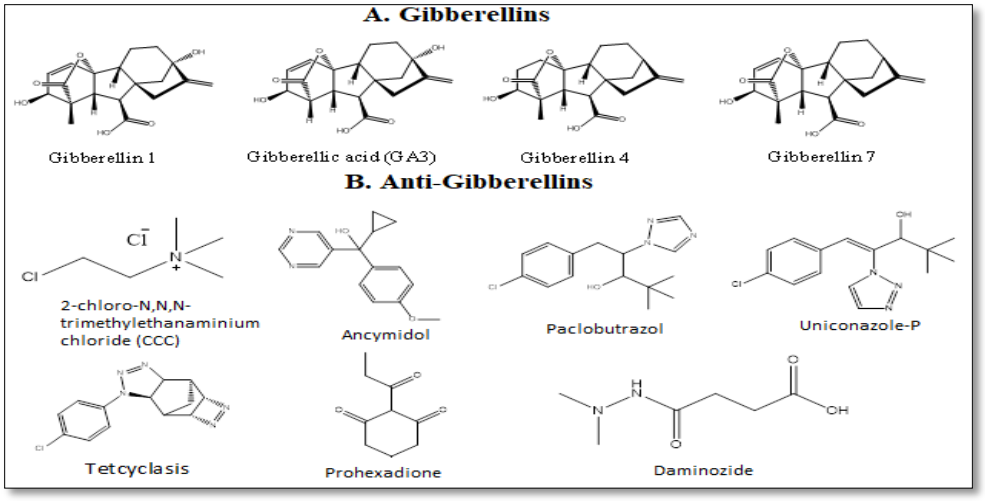

Figure 1. Gibberellins and anti-gibberellins compared.

MATERIALS AND METHODS

Our work was conducted with DRAGON software (version 5.5, 2007) and Cambridge Soft ChemOffice (version 12, 2010) with ChemDraw and Chem3D. We calculated 212 molecular descriptors. SPSS (Version 8.0 for Windows, SPSS Inc., New York, NY) was used to perform t-tests (p=0.05). The overall coefficients of variation (OCV) were calculated as described by Lorenzo et al. [14] (standard deviation/average) * 100). We considered the average values of the two growth regulators compared (gibberellins and anti-gibberellins) to calculate the standard deviation and average. The higher the difference between gibberellins and anti-gibberellins, the higher is the OCV. A dendrogram was obtained after conducting a hierarchical cluster analysis with data of chemical molecular descriptors. All variables were standardized (0-1) [15]

RESULTS AND DISCUSSION

In spite of 48 out of 212 molecular descriptors showed statistically significant differences between gibberellins and anti-gibberellins **(Table 1)**, only 16 showed "High" OCVs (101.72 to 141.42%). Gibberellins have 14.3 times (2.00/0.14) more 7-membered rings, 14.3 times (2.00/0.14) more 9-membered rings, 7.4 times (5.25/0.71) more ring tertiary carbon (sp^3), 6.1 times (5.25/0.86) more terminal tertiary carbon (sp^3) and 6.0 times (1.75/0.29) more terminal quaternary carbon (sp^3) than anti-gibberellins. Also gibberellins usually have ring quaternary carbon (sp^3) and aliphatic secondary carbon (sp^2) while anti-gibberellins usually do not. On the other hand, anti-gibberellins generally have aromatic ratio, aromatic bonds, nitrogen atoms, chlorine atoms, halogen atoms, benzene-like rings, aromatic carbon (sp^2), unsubstituted benzene carbon (sp^2) and substituted benzene carbon (sp^2) while gibberellins usually do not.

With "Medium" OCVs (64.82 to 98.08%), some molecular descriptors also showed statistically significant differences between gibberellins and anti-gibberellins. Gibberellins averaged 5.54 times (15.00/2.71) more circuits, 4.26 times (5.50/1.29) more ring secondary carbon (sp^3), 4.23 times (3.00/0.71) more 5-membered rings, 3.45 times (1.00/0.29) more 8-membered rings, 3.45 times (1.00/0.29) more carboxylic acid (aliphatic), 3.45 times (1.00/0.29) more secondary alcohols, 3.52 times (2.50/0.71) more hydroxyl groups, 3.22 times (5.50/1.71) more oxygen atoms, 2.91 times (3.75/1.29) more double bonds, 2.91 times (2.50/0.86) more donor atoms for H-bonds (N and O), 2.80 times (1.29/0.46) more hydrophilic factor, 2.69 times (5.00/1.86) more rings, 5.00 times (0.10/0.02) less rotatable bonds fraction and 3.14 times (3.14/1.00) less rotatable bonds than anti-gibberellins **(Table 1)**.

Data of **Table 1**, used in the hierarchical cluster analysis, generated the dendrogram shown in **Figure 2**. The two groups of regulators were appropriately congregated in two independent branches. Molecular descriptors have been applied to describe biological activities in many studies [16,17] showing their applicability as an attractive tool for efficient (e.g.) drug design process. It has been studied the potential of innovative computational tools in processing of structurally complex natural products to predict their macromolecular targets and attempt to forecast their role in drug discovery. Rodrigues et al. [18] and Faulon et al. [19] proposed a unified method for predicting protein-chemical interactions based on the representation of a protein using its atomistic structure. There are models that are useful in identifying compounds with potential risk of inhibiting the CYP3A4 enzyme. Arimoto et al. [20] and Kombo et al. [21] showed that shape-based descriptors ROG and SXL correlate with off-target activity and solubility, which in turn influence clinical success. They searched a potential

correlation between these shape-based descriptors and clinical success. With the rapid growth of public biological databases and biology-related web resources, abundant bioactivity data of small molecules and their targets are now available to the entire research community [22].

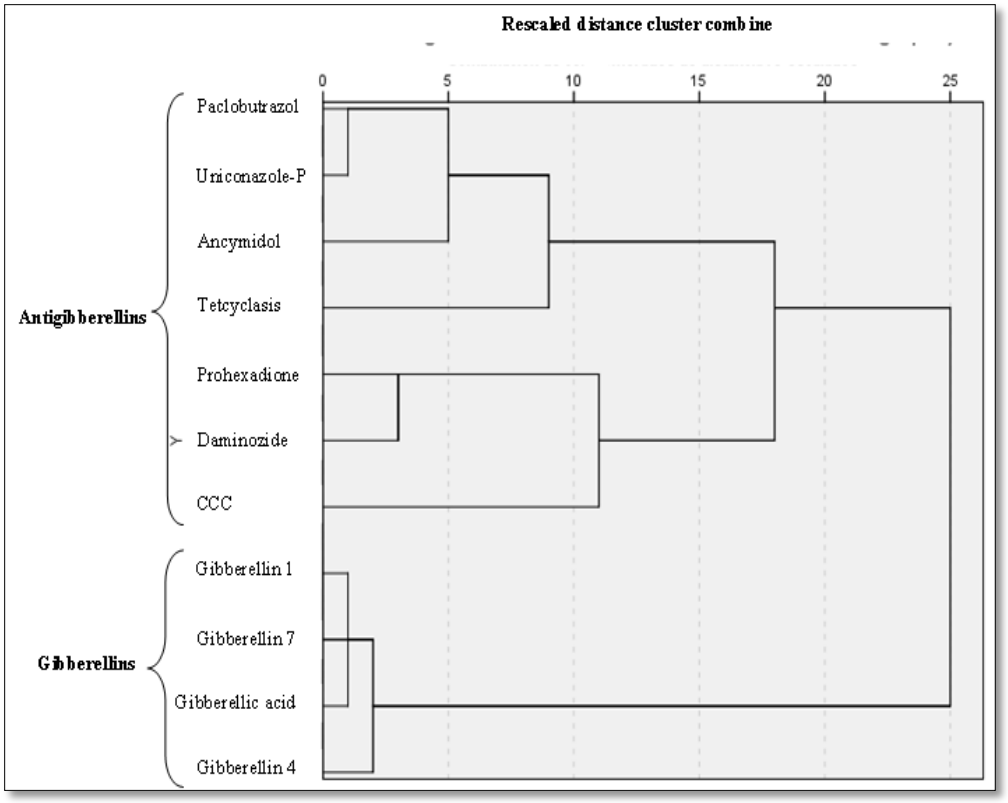

Figure 2. Hierarchical cluster analysis using the molecular descriptors for gibberellins and anti-gibberellins. Only those descriptors with statistical significant differences between gibberellins and anti-gibberellins were included **(Table 1)**. The dendogram was built using average linkage (between groups). Variables were standardized to vary from 0 to 1 according to Kantardzic [15].

From the biochemical point of view, it is important to note that it is not possible to justify dissimilarities between different compounds that act completely different. Gibberellins are hormones and these molecules are only active in plants if they link to its receptor so its role is very specific and this specificity is due to the structure of this molecule [16]. On the other hand, the anti-gibberellins studied here are compounds that act directly in the action of some enzymes involved in gibberellins biosynthesis. So, in this case, it does not matter their structure as there is no connection with gibberellin receptors and whatever the structure of these compounds, they act blocking enzymes from gibberellin biosynthesis [10,13].

However, the procedure described here is effective to differentiate (chemically) gibberellins and anti-gibberellins. New potential growth regulators can be identified, although this preliminary result should be later tested experimentally. A similar chemo-informatic procedure was previously used by our group to compare auxins, cytokinins and gibberellins; although different molecular descriptors were analyzed [23-25].

Table 1. Comparison of molecular descriptors for gibberellins and anti-gibberellins.

	Gibberellins				Anti-gibberellins									
	GA1	**GA3**	**GA4**	**GA7**	**CCC**	**Ancymidol**	**Paclobutrazol**	**Uniconazole-P**	**Tetcyclasis**	**Prohexadione**	**Daminozide**	**Gibberellins (average ± SE)** [1,3]	**Anti-gibberellins (average ± SE)** [2,3]	**OCV**[4]	**Classification of OCV**[5]
Aromatic ratio	0	0	0	0	0	0.571	0.524	0.524	0.261	0	0	0.00 ± 0.00 b	0.27 ± 0.10 a	141.42	High
Number of aromatic bonds	0	0	0	0	0	12	11	11	6	0	0	0.00 ± 0.00 b	5.71 ± 2.15 a	141.42	High
Number of ring quaternary C (sp^3)	2	1	2	2	0	0	0	0	0	0	0	1.75 ± 0.25 a	0.00 ± 0.00 b	141.42	High
Number of nitrogen atoms	0	0	0	0	1	2	3	3	5	0	2	0.00 ± 0.00 b	2.29 ± 0.61 a	141.42	High
Number of chlorine atoms	0	0	0	0	1	0	1	1	1	0	0	0.00 ± 0.00 b	0.57 ± 0.20 a	141.42	High
Number of halogen atoms	0	0	0	0	1	0	1	1	1	0	0	0.00 ± 0.00 b	0.57 ± 0.20 a	141.42	High
Number of benzene-like rings	0	0	0	0	0	1	1	1	1	0	0	0.00 ± 0.00 b	0.57 ± 0.20 a	141.42	High
Number of aromatic C (sp^2)	0	0	0	0	0	10	8	8	6	0	0	0.00 ± 0.00 b	4.57 ± 1.67 a	141.42	High
Number of unsubstituted benzene C (sp^2)	0	0	0	0	0	4	4	4	4	0	0	0.00 ± 0.00 b	2.29 ± 0.81 a	141.42	High

Number of 5-membered rings	Number of ring secondary C (sp^3)	Rotatable bond fraction	Number of circuits	Number of terminal quaternary C (sp^3)	Number of terminal tertiary C (sp^3)	Number of ring tertiary C (sp^3)	Number of 9-membered rings	Number of 7-membered rings	Number of aliphatic secondary C (sp^2)	Number of substituted benzene C (sp^2)
3	5	0.020	15	2	5	5	2	2	2	0
3	5	0.021	15	1	6	6	2	2	2	0
3	7	0.019	15	2	5	5	2	2	0	0
3	5	0.020	15	2	5	5	2	2	2	0
0	0	0.053	0	0	0	0	0	0	0	0
0	2	0.108	3	0	2	1	0	0	0	2
1	0	0.122	2	1	0	0	0	0	0	2
1	0	0.103	2	1	0	0	0	0	0	2
3	5	0.029	11	0	2	2	1	1	0	2
0	2	0.111	1	0	2	2	0	0	0	0
0	0	0.182	0	0	0	0	0	0	0	0
3.00 ± 0.00 a	5.50 ± 0.50 a	0.02 ± 0.00 b	15.00 ± 0.00 a	1.75 ± 0.25 a	5.25 ± 0.25 a	5.25 ± 0.25 a	2.00 ± 0.00 a	2.00 ± 0.00 a	1.50 ± 0.50 a	0.00 ± 0.00 b
0.71 ± 0.42 b	1.29 ± 0.71 b	0.10 ± 0.02 a	2.71 ± 1.44 b	0.29 ± 0.18 b	0.86 ± 0.40 b	0.71 ± 0.36 b	0.14 ± 0.14 b	0.14 ± 0.14 b	0.00 ± 0.00 b	1.14 ± 0.40 a
87.03	87.83	94.73	98.08	101.72	101.72	107.55	122.57	122.57	141.42	141.42
Medium	Medium	Medium	Medium	High	High	High	High	High	High	High

Number of terminal secondary C (sp^3)	Number of rings	Hydrophilic factor	Number of donor atoms for H-bonds	Number of double bonds	Number of rotatable bonds	Number of oxygen atoms	Number of hydroxyl groups	Number of secondary alcohols	Number of carboxylic acid (aliphatic)	Number of 8-membered rings
5	5	1.638	3	4	1	6	3	1	1	1
5	5	1.670	3	4	1	6	3	1	1	1
7	5	0.927	2	3	1	5	2	1	1	1
5	5	0.927	2	4	1	5	2	1	1	1
0	0	0.004	0	0	1	0	0	0	0	0
2	3	0.371	1	0	4	2	1	0	0	0
3	2	0.401	1	0	5	1	1	1	0	0
1	2	0.401	1	1	4	1	1	1	0	0
5	5	0.000	0	2	1	0	0	0	0	2
3	1	0.538	1	4	3	5	1	0	1	0
2	0	1.508	2	2	4	3	1	0	1	0
5.50 ± 0.50 a	5.00 ± 0.00 a	1.29 ± 0.20 a	2.50 ± 0.29 a	3.75 ± 0.25 a	1.00 ± 0.00 b	5.50 ± 0.29 a	2.50 ± 0.29 a	1.00 ± 0.00 a	1.00 ± 0.00 a	1.00 ± 0.00 a
2.29 ± 0.61 b	1.86 ± 0.67 b	0.46 ± 0.19 b	0.86 ± 0.26 b	1.29 ± 0.57 b	3.14 ± 0.59 a	1.71 ± 0.68 b	0.71 ± 0.18 b b	0.29 ± 0.18 b	0.29 ± 0.18 b	0.29 ± 0.29 b
58.38	64.82	67.04	69.21	69.21	73.15	74.21	78.57	78.57	78.57	78.57
Low	Medium	Medium	Medium	Medium	Medium	Medium	Medium	Medium	Medium	Medium

Numb of non-N atoms	Sum of conventional bond orders (H-depleted)	Number of acceptor atoms for H-bonds (N, O, F)	Number of bonds	Sum of Kier-Hall electrotopological states	Number of carbon atoms	Number of non-H bonds	Topological polar surface area using	Topological polar surface area using	Number of 6-membered rings
25	33	6	51	65.83	19	29	104.06	104.06	2
24	32	6	48	63.92	18	28	104.06	104.06	2
24	31	5	52	58.92	19	28	83.83	83.83	2
24	32	5	50	59.92	19	28	83.83	83.83	2
7	6	0	19	14.61	5	6	0	0	0
19	27	4	37	42.80	15	21	55.24	55.24	2
20	26.5	3	41	44.86	15	21	50.94	50.94	1
20	27.5	3	39	45.69	15	21	50.94	50.94	1
19	28	5	35	38.94	13	23	52.68	52.68	2
15	19	5	27	49.83	10	15	88.51	88.51	1
11	12	5	22	34.83	6	10	69.64	69.64	0
24.25 ± 0.25 a	32.00 ± 0.41 a	5.50 ± 0.29 a	50.25 ± 0.85 a	62.15 ± 1.64 a	18.75 ± 0.25 a	28.25 ± 0.25 a	93.95 ± 5.84 a	93.95 ± 5.84 a	2.00 ± 0.00 a
15.86 ± 1.93 b	20.86 ± 3.34 b	3.57 ± 0.69b	31.43 ± 3.29 b	38.79 ± 4.43 b	11.29 ± 1.64 b	16.71 ± 2.48 b	52.56 ± 10.19 b	52.56 ± 10.19 b	1.00 ± 0.31 b
29.59	29.81	30.07	32.59	32.72	35.15	36.28	39.94	39.94	47.14
Low	Low	Low	Low	Low	Low	Low	Low	Low	Low

Ghose-Crippen molar refractivity	Molecular weight	Number of hydrogen atoms	Sum of atomic polarizabilities (scaled on carbon atom)	Sum of atomic van der Waals volumes (scaled on carbon atom)	Number of atoms	Sum of atomic Sanderson Electronegativities (scaled on carbon
86.414	346.41	22	30.10	28.65	47	47.68
81.913	332.38	20	28.34	27.05	44	44.80
84.078	332.43	24	30.41	28.73	48	48.24
84.887	330.41	22	29.65	28.13	46	46.36
32.130	122.64	13	11.81	10.58	20	19.67
72.148	256.33	16	23.25	22.20	35	35.04
81.795	293.83	20	26.18	24.57	40	39.91
83.946	291.81	18	25.42	23.98	38	38.03
77.388	273.75	12	21.93	21.06	31	31.37
49.650	212.22	12	16.84	16.15	27	27.94
38.851	160.20	12	13.18	12.51	23	23.60
84.32 ± 0.94 a	335.41 ± 3.70 a	22.00 ± 0.82 a	29.63 ± 0.46 a	28.14 ± 0.39 a	46.25 ± 0.85 a	46.77 ± 0.77 a
62.27 ± 8.16 b	230.11 ± 25.46 b	14.71 ± 1.25 b	19.80 ± 2.21 b	18.72 ± 2.13 b	30.57 ± 2.87 b	30.79 ± 2.83 b
21.27	26.33	28.06	28.11	28.42	28.86	29.13
Low	Low	Low	Low	Low	Low	Low

[1] Average information of GA1, GA3, GA4 and GA7

[2] Average information of 2-chloro-N,N,N-trimethylethanaminium chloride; ancymidol; paclobutrazol; uniconazole-P; tetcyclasis; prohexadione and daminozide

[3] Results with the same letter are not statistically different (t-test, $p>0.05$)

[4] Overall coefficient of variation = (Standard deviation/Average)*100. To calculate this coefficient. Average values of gibberellins and anti-gibberellins were considered The higher the difference between these two averages, the higher the overall coefficient of variation

[5] Classification of OCVs: ¨Low¨ from 21.27 to 58.38%; ¨Medium¨ from 64.82 to 98.08% and ¨High¨ from 101.72 to 141.42%

GA1: Gibberellin 1; GA3: Gibberellic acid; GA4: Gibberellin 4; GA7: Gibberellin 7; CCC: 2-chloro-N,N,N-trimethylethanaminium chloride; ancymidol; paclobutrazol; uniconazole-P; tetcyclasis; prohexadione and daminozide

AUTHOR CONTRIBUTION

I.A., D.G., L.P. and J.C.L. designed the research, analyzed the data and wrote the paper. J.C.L. had primary responsibility for the final content. All authors have read and approved the final manuscript.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest

Authors do not have any conflict of interests.

REFERENCES

1. Salisbury FB, Ross CW (1992) Plant Physiology (In Spanish). Wadsworth Publishing, California.
2. Machakova I, Zazimalova E, George EF (2008) Plant growth regulators I: Introduction; auxins, their analogues and inhibitors. In: George EF, Hall M, De Kerk GJ (eds) Plant Propagation by Tissue Culture. Springer, Dordrecht, pp: 175-204.
3. Lorenzo JC, González B, Escalona M, Teisson C, Espinosa P, et al. (1998) Sugarcane shoot formation in an improved temporary immersion system. Plant Cell Tissue Organ Cult 54: 197-200.
4. Escalona M, Lorenzo JC, González B, Daquinta M, Borroto C, et al. (1999) Pineapple micropropagation in temporary immersion systems. Plant Cell Rep 18: 743-748.
5. Ali S, Khan N, Nouroz F, Erum S, Nasim W, et al. (2018) *In vitro* effects of GA3 on morphogenesis of CIP potato explants and acclimatization of plantlets in field. In Vitro Cell Dev Biol Plant, pp: 1-8.
6. dos Santos DS, Cardoso-Gustavson P, Nievola CC (2017) Stem elongation of ornamental bromeliad in tissue culture depends on the temperature even in the presence of gibberellic acid. Acta Physiol Plant 39: 230.
7. Zhao D, Xue Y, Shi M, Tao J (2017) Rescue and in vitro culture of herbaceous peony immature embryos by organogenesis. Sci Hort 217: 123-129.
8. Buhl C, Strauss S, Lindroth R (2018) Genetic down-regulation of gibberellin results in semi-dwarf poplar but few non-target effects on chemical resistance and tolerance to defoliation. J Plant Ecol.
9. Murcia G, Pontin M, Piccoli P (2018) Role of ABA and Gibberellin A3 on gene expression pattern of sugar transporters and invertases in *Vitis vinifera* cv. Malbec during berry ripening. Plant Growth Regul 84: 275-283.
10. Moshkov IE, Novikova GV, Hall MA, George EF (2008) Plant growth regulators III: Gibberellins, ethylene, abscisic acid, their analogues and inhibitors; miscellaneous compounds. In: George EF, Hall MA, de Kerk GJ (eds) Plant Propagation by Tissue Culture. Springer, Dordretch, pp: 227-282.
11. Zhang H, Ma ZF, Yang H, Kong L (2017) Determination of chlormequat and mepiquat residues and their dissipation rates in tomato cultivation matrices by ultra-performance liquid chromatography-tandem mass spectrometry. J Chrom B 1064: 75-84.
12. Verma A, Jain N, Kaur B (2010) Regulation of plant behavior through potential anti-gibberellins compounds. J Plant Sci Res 26: 227.
13. Kavalier AR, Pitra NJ, Koelling JM, Coles MC, Kennelly EJ, et al. (2011) Increase in cone biomass and terpenophenolics in hops (*Humulus lupulus* L.) by treatment with prohexadione-calcium. J Agric Food Chem 59: 6720-6729.
14. Lorenzo JC, Yabor L, Medina N, Quintana N, Wells V (2015) Coefficient of variation can identify the most important effects of experimental treatments. Notulae Botanicae Horti Agrobotanici Cluj-Napoca 43: 287-291.
15. Kantardzic M (2003) Data mining: Concepts, models, methods and algorithms. Wiley, New Jersey.
16. Casañola-Martin GM, Khan MTH, Marrero-Ponce Y, Ather A, Sultan S, et al. (2007) TOMOCOMD-CARDD descriptors-based virtual screening of tyrosinase inhibitors. 1. Evaluation of different classification model combinations using group, atom-type and total bilinear indices. Bioorg Med Chem 15: 1483-1503.
17. Dieguez-Santana K, Pham-The H, Rivera-Borroto OM, Puris A, Thi-Thu HL, et al. (2017) A two QSAR way for anti-diabetic agents targeting using α-amylase and α-glucosidase inhibitors: Model parameters settings in artificial intelligence techniques. Lett Drug Des Disc 14: 862-868.
18. Rodrigues T, Reker D, Schneider P, Schneider G (2016) Counting on natural products for drug design. Nat Chem 8: 531-541.
19. Faulon JL, Misra M, Martin S, Sale K, Sapra R (2008) Genome scale enzyme-metabolite and drug-target interaction predictions using the signature molecular descriptor. Bioinformatics 24: 225-233.
20. Arimoto R, Prasad MA, Gifford EM (2005) Development of CYP3A4 inhibition models: Comparisons of machine-learning techniques and molecular descriptors. J Biomol Screen 10: 197-205.
21. Kombo DC, Tallapragada K, Jain R, Chewning J, Mazurov AA, et al. (2012) 3D molecular descriptors

important for clinical success. J Chem Inf Model 53: 327-342.

22. Lavecchia A, Cerchia C (2016) *In silico* methods to address polypharmacology: Current status, applications and future perspectives. Drug Discov Today 21: 288-298.

23. Andújar I, Gómez D, Pérez L, Lorenzo JC (2018) Use of chemo-informatics to identify molecular descriptors of auxins, cytokinins and gibberellins. J Appl Bioinforma Comput Biol 7: 2.

24. Pham-The H, Casañola-Martin GM, Dieguez-Santana K, Hai NN, Ngoc NT, et al. (2017) Quantitative structure-activity relationship analysis and virtual screening studies for identifying HDAC2 inhibitors from known HDAC bioactive chemical libraries. SAR QSAR Environ Res 28: 199-220.

25. van Staden J, Zazimalova E, George EF (2008) Plant growth regulators II: Cytokinins, their analogues and antagonists. In: George EF, Hall M, De Kerk GJ (eds) Plant Propagation by Tissue Culture. Springer, Dordrecht, pp: 205-226.