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Revisión / Review

Ipomoea batatas (L.) Lam. (Convolvulaceae) as a source of polyphenols with antitumor activity and prospects for *in vitro* production using chemical elicitors - A Review

[*Ipomoea batatas* (L.) Lam. (Convolvulaceae) como fuente de polifenoles con actividad antitumoral y perspectivas de su producción *in vitro* utilizando elicitores químicos – Una Revisión]

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Section Review

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Abstract: *Ipomoea batatas* has an enormous projection as functional food and it is an excellent source of anticancerous or chemopreventive substances. Plant tissue culture offers the possibility of inducing secondary metabolites production under controlled conditions and their projection for industrial purposes. To establish the state of knowledge regarding advances in polyphenols chemical elicitation from *I. batatas* and the possibility of producing potential anticancerous compounds *in vitro* culture systems, a bibliometric review and an analysis of information available until 2020 were made. Results showed that research field on which review was carried out is current and has a growing trend; however, sweet potato cell suspensions evaluation is scarce. Elicitation using compounds with hormonal effects represents a good alternative to increase phenolic acids production in this species. Advances in phenols elicitation from sweet potato cell suspensions will require search superior genotypes, and associating this knowledge with *in vivo* and *in silico* studies.

Keywords: Cancer; Phenolic acids; Cell suspensions; Sweet potato; Secondary metabolites.

Resumen: *Ipomoea batatas* tiene una enorme proyección como alimento funcional y es una excelente fuente de sustancias anticancerosas o quimiopreventivas. El cultivo de tejidos vegetales ofrece la posibilidad de inducir la producción de metabolitos secundarios en condiciones controladas y su proyección con fines industriales. Para establecer el estado del conocimiento sobre los avances en la elicitación química de polifenoles en *I. batatas* y la posibilidad de producir compuestos potencialmente anticancerosos en sistemas de cultivo *in vitro*, se realizó una revisión bibliométrica y un análisis de la información disponible hasta 2020. Los resultados mostraron que el campo de investigación en el que se realizó la revisión es actual y tiene una tendencia creciente; sin embargo, la evaluación de las suspensiones celulares de batata es escasa. La elicitación usando compuestos con efectos hormonales representa una buena alternativa para incrementar la producción de ácidos fenólicos en esta especie. Los avances en la obtención de fenoles a partir de suspensiones celulares de batata requerirán la búsqueda de genotipos superiores y la asociación de este conocimiento con estudios *in vivo* e *in silico*.

Palabras clave: Cáncer; Ácidos fenólicos; Suspensiones celulares; Batata; Metabolitos secundarios.

INTRODUCTION

Many nontransmissible diseases are initiated by free radicals formation in the mitochondria during ATP production which, like other substances of similar nature, alter living tissues metabolism, influencing cell growth and development, increasing aging, and promoting cancer and inflammatory diseases incidence (Li *et al*., 2020). In anticancer campaigns, several diet natural components have been proposed as chemopreventive and *in vitro* screening of crude plant extracts or their fractions is considered as a crucial step in finding more effective agents to reduce oxidative stress and cancer (Naz *et al*., 2017; Mustafa *et al*., 2021).

Drug resistance has been evidenced in tumor lines and chemotherapy is less and less efficient (Min *et al*., 2018; Abotaleb *et al*., 2020). Resistance to drugs such as sorafenib and cisplatin has been related with alterations in cellular transporters, polymorphisms, and mutations in key genes of cancer-associated signaling pathways (Cabral *et al*., 2020), while resistance to paclitaxel may be influenced due to its frequent use and inhibition of apoptotic pathways activation (Zhang *et al*., 2012). On the other hand, resistance to anastrozole is due to chronic estrogen receptors stimulation by low levels of estradiol (Mehta *et al*., 2019).

About 70% of anticancerous agents used currently come from natural sources, mainly from plant species or from their derivatives (Twilley *et al*., 2020); for this reason use of plants with medicinal potential in biotechnological processes constitutes a developing field. Natural medicines have an effect on multiple therapeutic targets, which allows them to effectively compensate for the biological complexity of cancer (Ma *et al*., 2021). Polyphenols act on several targets involved in cancer appearance and progression, through mechanisms that involve cell cycle arrest, apoptosis, and angiogenesis inhibition (Abbaszadeh *et al*., 2019; Sarma *et al*., 2019), which would possibly allow them to counteract drug resistance present in cancer cells.

Ipomoea batatas (L.) (sweet potato) belongs to Convolvulaceae and grows in Central and South America. This species has spread throughout the world as a result of its adaptability to a large number of environmental conditions and its resistance to pests and diseases (Roullier *et al*., 2013; Katayama *et al*., 2017; Jackson *et al*., 2020). Sweet potato growing is located in third place among root and tuber crops, only surpassed by potatoes and cassava, and reaches position 15 considering the main crops in world, with a total of 8,062,735 ha harvested and a production of 91,945,358 tons in 2018 (FAO, 2020).

Sweet potato medicinal properties are well documented, highlighting their anti-inflammatory, antitumorous, antidiabetic, antioxidant and antimutagenic activity; these have been related to their high polyphenol concentrations (Hue *et al*., 2011; Mohanraj & Sivasankar, 2014; Naz *et al*., 2017; Katayama *et al*., 2017; Dinu *et al*., 2018; Sun *et al*., 2019; Islam, 2019), which in turn coincides with those evidenced in other members of Convolvulaceae. Plants can be used as taxonomic markers in search for new bioactive substances (Omotayo & Borokini, 2012); in this sense, some species related to sweet potato, such as *Merremia emarginata* (Burm. F.), *M. mammosa* (Lour.) Hallier f., *I. carnea* Jacq. and *M. aegyptia* (L.) Urb. have been studied, and extracts bioactivity is attributed mainly to presence of phenolic compounds (Joshi *et al*., 2015; Angappan *et al*.; 2018; Khan *et al*., 2018; Ratnadewi *et al*., 2020, Jeyadevi *et al*., 2019).

Although phenols share their basic structure (at least one aromatic ring with one or more hydroxyl groups), variations of each compound or subfamily determine their mechanism of action in relation to their bioactivity (Abotaleb *et al*., 2020; Zhang *et al*., 2020). Thus, diversity in specific structures gives polyphenols the possibility of regulating multiple targets in ways that lead to appearance of cancer or its progression, both directly, through production of ROS, or indirectly, as gene expression regulators (Fantini *et al*., 2015; Abotaleb *et al*., 2020; Bian *et al*., 2020).

Sweet potato plants are rich in phenolic acids; however, assessment of polyphenols content in leaves and roots indicates that their concentration depends largely on aspects inherent to biology of the species, as well as on environmental factors and others such as crop management (Islam *et al*., 2002; Dini *et al*., 2006; Naz *et al*., 2017; Kobayashi *et al*., 2019; Sun *et al*., 2019). Therefore, establishment of sweet potato plantations to produce bioactive compounds of commercial interest would require availability of large plantations to supply only a part of demand for this type of substances.

Field production of sweet potato involves maintenance activities typical of crop, large areas of land, diseases or pathogens control in planting material, and variation in content of compounds of interest during a year (Acedo, 2015; Kobayashi *et al*., 2019; Suárez *et al*., 2020). Knowing that roots and tubers are staple foods in developing countries and

that sweet potato has become a crop with great potential to fight against hunger in Asian countries (Acedo, 2015; Katayama *et al*., 2017), food security of vulnerable populations could be negatively affected if sweet potato is not considered mainly as a food product and instead they make use of leaf even when the root is not yet ready to be harvested.

In the previously described context, a plant tissue culture is a good alternative aimed at sustained production of polyphenols starting from little initial material independently of environmental factors that cannot be controlled in field crops (Dias *et al*., 2016; Thakur *et al*., 2018; Efferth, 2019), and simultaneously reducing costs and time in development of new drugs from indigenous plant materials (Wang *et al*., 2017a). In addition, antioxidants produced in this way are more attractive than those obtained by chemical synthesis; severe toxicity has been evidenced in the latter due to their long-term consumption (genotoxicity, carcinogenicity and hepatotoxicity) (Naz *et al*., 2017), also higher costs and less effectiveness (Chandran *et al*., 2020).

Polyphenols with high bioactivity production from cultured sweet potato tissues is promising given the fact that their foliar extracts have shown an antioxidant activity greater (values up to 8.3 times higher) than gallic acid, butylated hydroxytoluene (BHT) and ascorbic acid (Nagai *et al*., 2011). Although it is possible to obtain phenolic compounds in cell suspensions only by guaranteeing cells survival, elicitation is always necessary if any secondary metabolite production from them is to be increased (Wang *et al*., 2017a).

A wide variety of biotic and abiotic factors have been successfully tested when obtaining metabolites of interest. In polyphenols production although there are many pieces of information on use of various types of elicitors, manipulation of light conditions continues to be the factor that has received most attention due to stress it produces in plants, as can be evidenced in the review by Dias *et al*. (2016). Even so, elicitation with chemical/hormonal substances is of particular interest and is a field that deserves further exploration.

LITERATURE REVIEW

This bibliographic review adopts the approach of PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (2020) and is directed to show the potential of sweet potato in polyphenols with antitumorous activity production by means of establishment of cell suspensions stimulated with chemical elicitors. The Documentary Review and Analysis (DRA) methodology (Barbosa *et al*., 2013) was used, through search and systematic review of scientific articles in databases (Scopus, National Center for Biotechnology Information (NCBI) - PubMed, PubChem and Web of Science, mainly published), until 2020, and in scientific collaboration networks (ResearchGate). Generation of data network maps and establishment of relationships among terms by means of bibliometric analysis with the VOSviewer v. 1.6.16 tool were also prepared.

Two search equations were used. With equation 1: "TITLE-ABS-KEY ("Ipomoea batatas" OR batat OR sweetpotato OR "sweet potato" OR batata OR camote OR boniato) AND (polyphenol* OR phenol* OR "phenolic acid" OR anthocyanin*) AND (bioactiv* OR antioxid* OR "scavenging activity" OR antimutagenic OR antiprolif* OR tumor* OR cancer))", information on extracts of sweet potato bioactivity in relation to their phenolic content was obtained, while equation 2: "TITLE-ABS-KEY((phenol* OR fenol* OR phenylpropanoid) AND (polyphenol* OR anthocyanin* OR flavonoid* OR "phenolic acid*") AND ("In vitro culture" OR "plant cell culture" OR "celular suspension*" OR callus OR calli) AND (elicit* OR stress))" was used to estimate usage of techniques of plant tissue culture in phenols production.

RESULTS (Bibliometric data)

Bioactivity and phenolic content of sweet potato *extracts*

According to results obtained, publications associated with the search terms of equation 1 spanned from 1984 to 2020. Figure No. 1 shows that there is a growing interest in the subject under study in this review, which is more noticeable in the last two decades. The database that produced the highest number of total publications was Web of Science with 579 results, followed by Scopus with 527 results; PubMed was the database with the lowest number of publications, with a total of 213.

It was found that Asian countries are the largest producers of information on the subject; China (31.43%), Japan (11.05%), South Korea (8.46%), and Taiwan (5.18%) report the highest percentages. However, as shown in Figure No. 2, some American countries take important places in this list, such as USA in second place (13.47%), and Brazil in tenth place (2.76%). The remaining part of

bibliographic production is distributed among other Asian countries (India, Pakistan, Indonesia and Malaysia), some European countries (Italy, Spain and Portugal) and some African countries (South Africa and Nigeria); however, in any case the percentage related to total number of publications is higher than 4%.

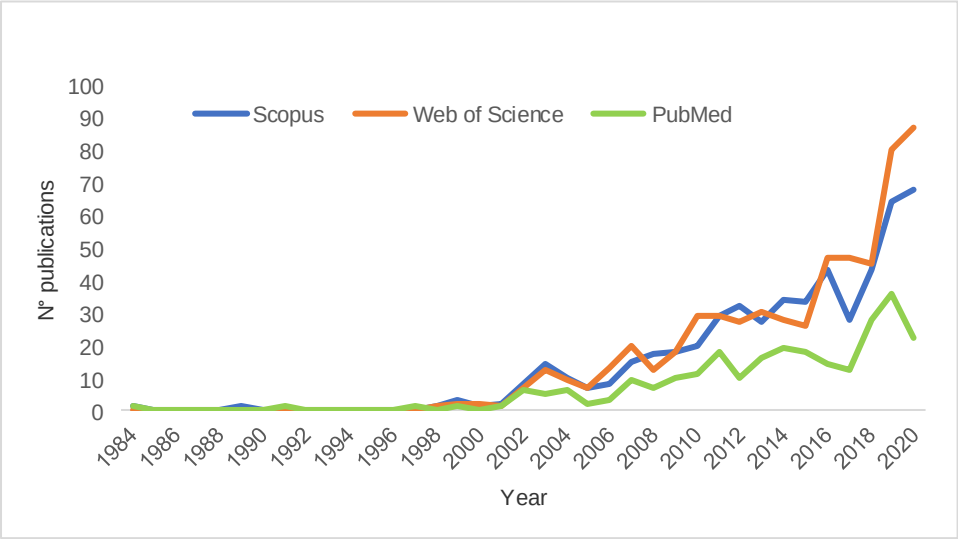

Figure No. 1
Number of publications per year in the three main databases consulted, using search equation 1

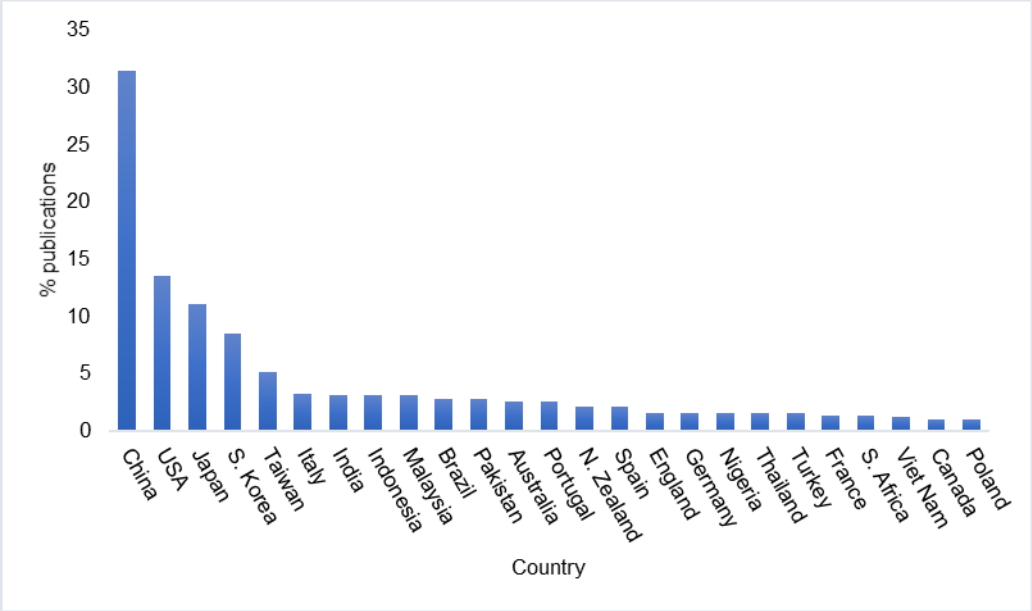

Figure No. 2
Percentage of publications by country in the three main databases consulted, using search equation 1

Despite difference in number of results found in each database, term association analysis using the results of each search was very similar. Figure No. 3 shows a marked relationship between sweet potato and its antioxidant activity, in addition to other types of biological activity such as anti-tumorous and anti-inflammatory activities, although to a lesser extent. Likewise, bioactivity of sweet potato is directly related to polyphenols concentration and other substances derived from them such as flavonoids, anthocyanins, and some phenolic acids. β-carotene is another important secondary metabolite, in part due to the fact that the highest commercial demand as a food varieties correspond to yellow and orange sweet potato, which are rich in this compound (Park *et al*., 2016).

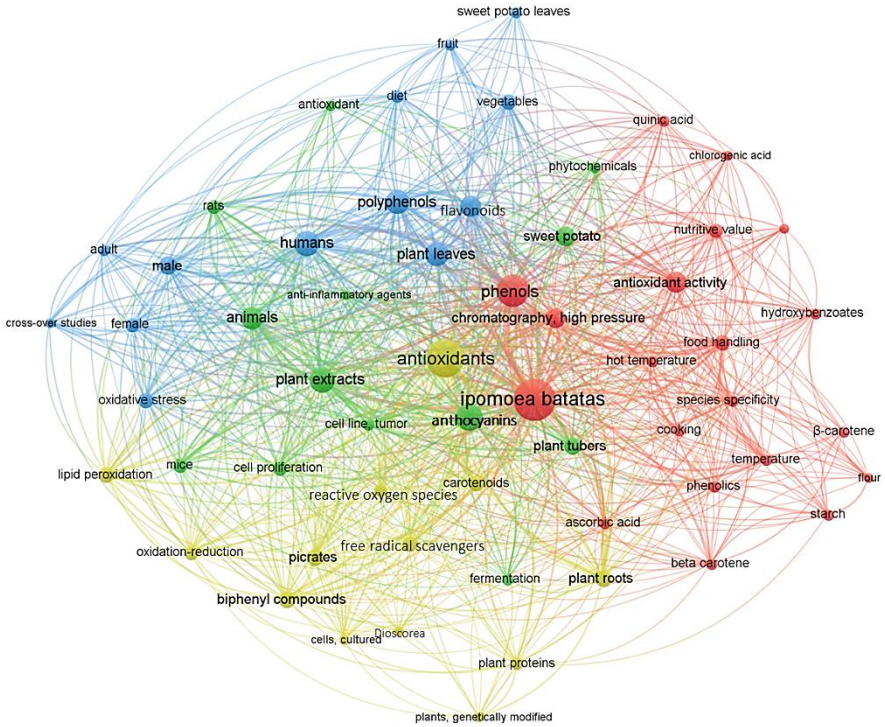

Figure 3
Association of terms análisis data map using results obtained with the search equation 1

Plant tissue culture in phenolic compounds production

Results obtained in databases when using equation 2 indicate existence of documents related to search terms since 1997; however, corresponding bibliographic production was scarce up to the first decade of 2000's, where there is evidence of a greater number of publications and also an upward trend in subsequent years, reaching its highest peak in 2019 (this applies for the three main databases consulted). Scopus, Web of Science and PubMed databases returned 218, 206, and 56 total results, respectively. It is noteworthy that number of publications related to search terms is increasing, plant tissue culture associated with production of phenolic-type secondary metabolites being a current topic of key importance as evidenced in Figure No. 4.

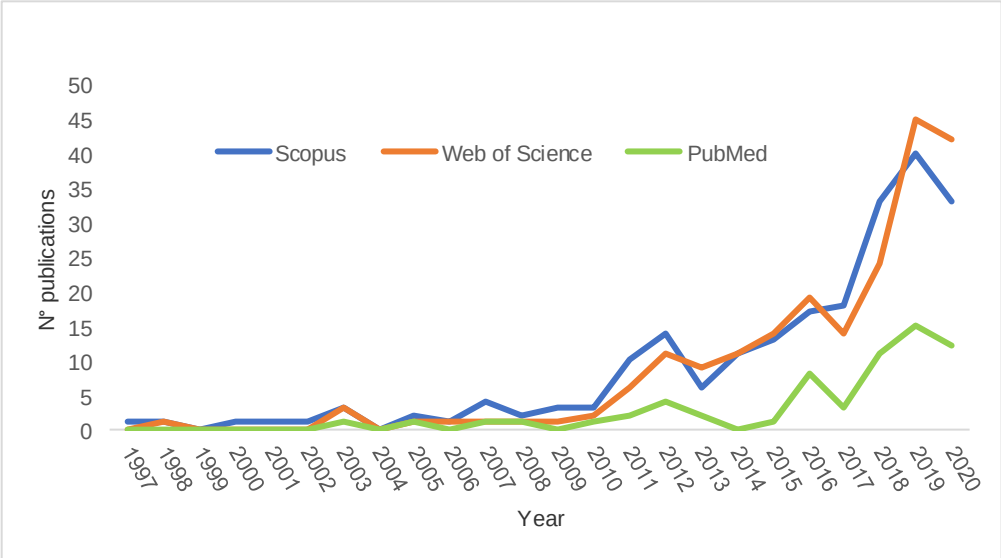

Figure No. 4
Number of publications per year in the three main databases consulted, using search equation 2

Distribution of publications by country is quite wide (47 countries). Figure No. 5 shows 30 countries with the highest number of publications on the subject, with Pakistan (16.05%), Iran (13.30%) and India (11.46%) having the highest percentages of publications associated with search terms; European countries such as Germany and France score 7.33 and 6.42% respectively. Latin American countries have a low participation: Mexico is in position 13 (3.21%), in addition to Brazil in position 21 and Colombia in position 24, respectively, both with less than 2% of the publications.

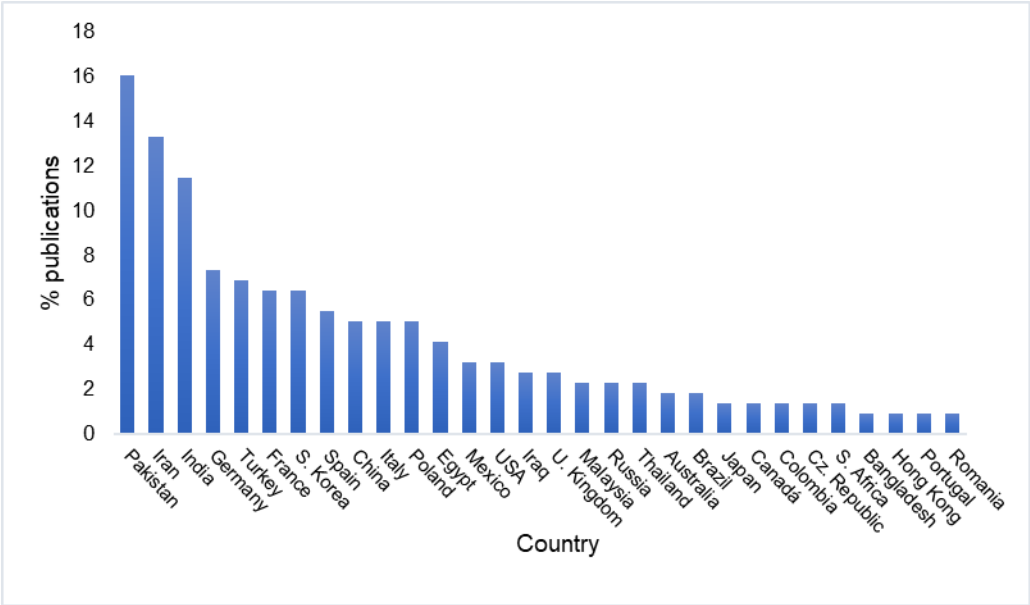

Figure No. 5
Percentage of publications by country in the three main databases consulted, using search equation 2

A certain degree of correspondence between plant tissue culture and phenolic compounds elicitation became noticeable by relating the most frequent terms in search results using the equation 2. Most frequent elicitors corresponded to jasmonates and salicylic acid (SA), while flavonoids were the most elicited group, followed by anthocyanins and phenolic acids. At the individual level, compounds such as resveratrol and chlorogenic acid have been of particular interest, which seems to be related mainly to their antioxidant activity (Figure No. 6).

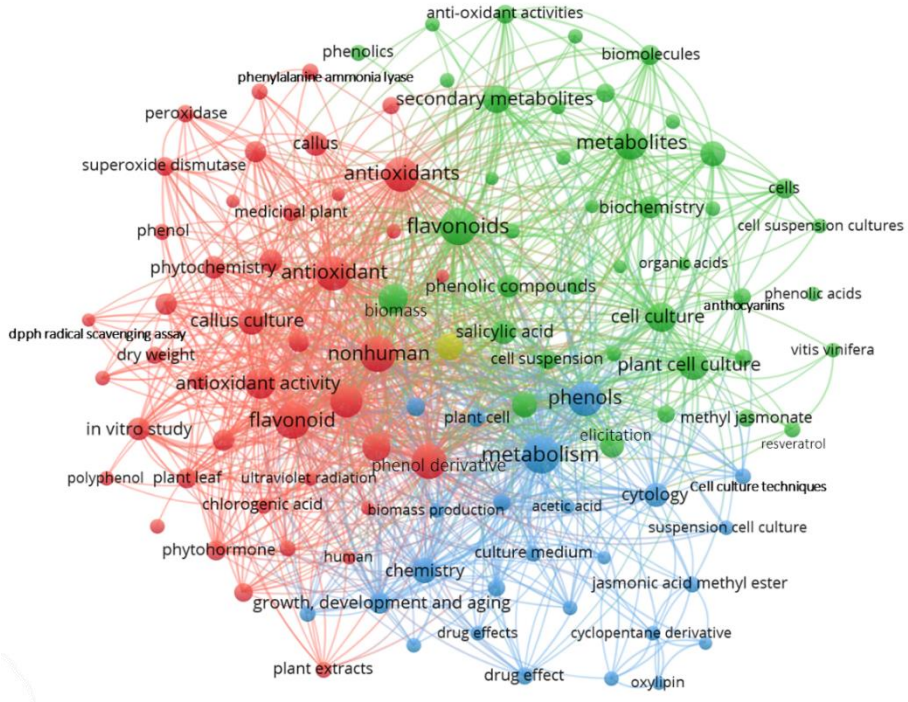

Figure 6
Association of terms analysis data map using results obtained with the search equation 2

DISCUSSION

Relationship between genetic diversity and phenolic content of sweet potato

Sweet potato is a typical plant of tropical regions, where it is cultivated due to its high content of carbohydrates and nutrients; mainly its roots are consumed; although, leaves are also used as a vegetable in Asian countries (Dinu *et al*., 2018). In this sense, edible organs of the plant have been studied in relation to their bioactive compounds content (mainly phenolic-type antioxidants). However, the data obtained varies highly due to wide genetic and morphological diversity within the species (Rosero *et al*., 2019; Jackson *et al*., 2020), which has been attributed to factors including its polyploid nature, high heterozygosity product of cross between varieties, and vegetative propagation (Tsutsui *et al*., 2016; Katayama *et al*., 2017).

Total number of sweet potato cultivars is difficult to estimate due to efforts that have been made (especially in Asian countries such as Japan) to produce and release new genotypes that meet direct consumers and industry demands (Katayama *et al*., 2017). According to Zhang *et al.* (2018), more than 2,000 varieties are grown in China and Jackson *et al.* (2020) indicate existence of an ample range, going from 20,000 to more than 35,000 sweet potato accessions among different research centers and institutions worldwide, which have not been fully characterized.

Sweet potato varieties, especially indigenous materials, are conventionally classified and

referenced according to root peel or root flesh colour (despite the fact that there are other morphoagronomic characteristics), constituting types rather than varieties as they are normally known. In this way, purple, white, yellow and orange sweet potatoes can be identified, including their various shades, as evidenced in the works by Tang *et al*. (2015), Zhang *et al*. (2018) and Sun *et al*. (2019).

Conventional sweet potato classification is confusing given the fact that eventually there is no coincidence between root peel colour and root flesh colour, giving rise to multiple combinations, as can be seen in Tsutsui *et al*. (2016). Despite the above, and as a strategy to counteract low diversity implied by asexual reproduction of this species (Drapal *et al*., 2019), a large number of sweet potato cultivars have been obtained, which are generally named using another typologies (a striking name, the last name of the breeder, cryptic codes [letters and numbers], among others). This has been done taking into account regulations designed or adopted by each country through competent bodies (governmental or not), which generally comply with the International Code of Nomenclature for Algae, Fungi and Plants (ICN) and the International Code of Nomenclature for Cultivated Plants (ICNCP) (ISHS, 2016).

When comparing total polyphenol content (TPC) in leaves of different sweet potato genotypes, expressed as gallic acid equivalent (GAE) or chlorogenic acid equivalent (CAE) per 100 g of dry mass (DM), reported values vary between 1.42 and 17.1 g GAE/CAE (Islam *et al*., 2002; Yoshimoto *et al*., 2002; Islam *et al*., 2009; Nagai *et al*., 2011; Sun *et al*., 2014; Islam, 2019; Kobayashi *et al*., 2019; Suárez *et al*., 2020), as shown in Figure 7. However, there are reports exhibiting lower TPC values. Ghasemzadeh *et al*. (2012) evaluated TPC in leaves of six varieties of sweet potato and found that Vardaman variety (golden-skinned root, intense orange flesh) presented a higher content of these substances (8.11 mg GAE g^{-1}), while the lower content (4.47 mg GAE g^{-1}) was found in Centennial variety (faint yellow-skinned root, dark orange flesh).

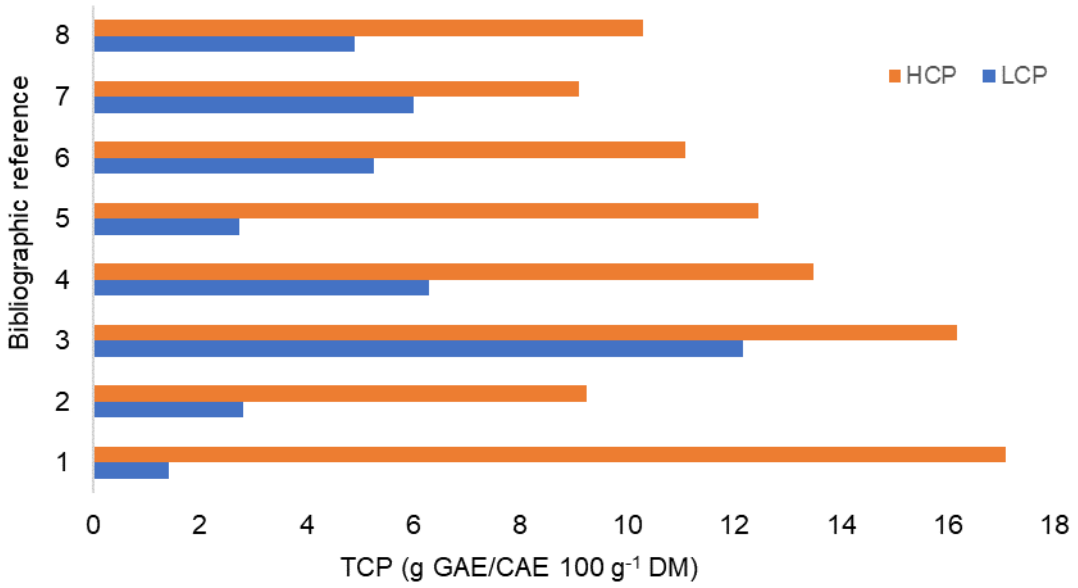

Figure No. 7
Sweet potato maximum (HCP) and minimum (LCP) total polyphenol content, reported in various bibliographic references: 1. Islam *et al.* (2002), 2. Yoshimoto *et al.* (2002), 3. Islam *et al*. (2009), 4. Nagai *et al.* (2011), 5. Sun *et al.* (2014), 6. Islam (2019), 7. Kobayashi *et al.* (2019), 8. Suárez *et al.* (2020)

Tang *et al.* (2015) reported TPC in sweet potato in range of 4.15 - 16.8 mg GAE g^{-1} (in raw root samples), where varieties with purple and orange roots presented the highest concentrations, compared to varieties with roots with yellow and white coloration; Chao *et al.* (2014), using green and purple leaves of this species, found TPC of 18.17 and 22.8 mg GAE g^{-1}, respectively. Seasonal variation or harvest period effect has also been documented, values of 4.91 - 10.29 g EAC 100 g^{-1} DM (Kobayashi *et al*., 2019) and 6.0 - 9.1 g EAC 100 g^{-1} DM (Suárez *et al*., 2020) have been reported.

Phenols are abundant compounds in Convolvulaceae species and TPC recorded among them is determined by various factors; values of 5.9 to 30.35% have been found in *M. borneensis* (Hossain & Shah, 2015), from 0.62 to 2.81% in *I. reniformis* (Raghuvanshi *et al*., 2017), and from 2.31 to 35.99% in *M. mammosa* (Ratnadewi *et al*., 2020), depending on solvent used. Similarly, it has been shown that climatic periods can regulate phenols production in *M. aegyptia*, with TPC ranging from 0.32% to 6.03% (Salgado *et al*., 2020). On the other hand, variety can be an influencing factor in *I. aquatica* (TPC of 1.9 - 17.47%) (Lawal *et al*., 2016; Mariani *et al*., 2019).

Morphoagronomic sweet potato leaves and roots diversity makes it difficult to define criteria that allow identify, without a doubt, the variety that presents the greatest bioactive potential in relation to others. however, it has been established that varieties with purple-fleshed roots have regularly higher polyphenol content than varieties with roots flesh of other colors (such as yellow and white) (Chao *et al*., 2014; Tang *et al*., 2015; Zhang *et al*., 2018; Šlosár *et al*., 2020). When comparing polyphenols concentration, as well as antioxidant and antiproliferative activites of sweet potato extracts, it is evident that aforementioned variables not only depend on genotype of the plant, but are highly influenced by used organ (even between parts of the same organ, such as roots peel and roots flesh, or leaf blade and petiole), collection time, solvent, extraction conditions, and quantification method (Islam *et al*., 2002; Naz *et al*., 2017; Dinu *et al*., 2018; Kobayashi *et al*., 2019; Sun *et al*., 2019).

Polyphenols that have been identified in sweet potato extracts, regardless of organ, correspond mainly to anthocyanins and phenolic acids (Konczak *et al*., 2003a; Tang *et al*., 2015; Islam, 2019). Among the compounds belonging to this last group caffeic acid, chlorogenic acid and their derivatives are included (Islam *et al*., 2002; Kobayashi *et al*., 2019; Rashmi & Negi, 2020), and 4,5 di-caffeoylquinic and 3,4,5-tri-caffeoylquinic acids deserving special mention for their antioxidant and antimutagenic activities. Thus, phenolic acids are considered good candidates for both prevention as well as cancer treatment (Islam *et al*., 2009; Islam, 2019; Zhang *et al*., 2019).

In spite of the above, in sweet potato varieties with yellow and orange flesh, this bioactivity has been mainly associated with carotenoid content (Tang *et al*., 2015; Tanaka *et al*., 2017). Furthermore, ferulic acid, catechin, vanillic acid, quercetin, hyperoside, luteolin, myricetin, gallic acid, kaempferol, apigenin, morin, and rutin have also been detected as important compounds (Johnson & Pace, 2010; Chao *et al*., 2014; Ghasemzadeh *et al*. 2016; Ayeleso *et al*., 2018; Sun *et al*., 2019). Figure No. 8 and Table No. 1 show some phenolic compounds identified in sweet potato extracts and type of associated bioactivity.

Anticancerous potential of sweet potato extracts

Antioxidants can reduce the risk of suffering chronic diseases and those of natural origin offer a high prophylactic potential in diseases treatment due to oxidative damage (Naz *et al.*, 2017). Antitumorous potential of a substance has been related to its antioxidant or antimutagenic activity, which are documented for sweet potato. However, evaluations of anticancerous potential of this species using cell lines or *in vivo* models are still lacking and have emerged recently (Konczak *et al*., 2003a; Karna *et al*., 2011; Gundala *et al*., 2013).

Yoshimoto *et al.* (2002), indicates antimutagenic effect of phenolic acids present in different sweet potato varieties on mutation induced by 3-Amino-1,4-dimethyl-5H-pyrido [4,3- b] indole (Trp-P-1) inhibition on TA98 strain of *Salmonella typhimurium*. The author establishes the following order in terms of effectiveness: 3,4,5-tri-caffeoylquinic acid > 3,4-di-caffeoylquinic acid = 3,5-di-caffeoylquinic acid = 4,5-di-caffeoylquinic acid > chlorogenic acid. Similarly, Islam *et al.* (2019) draw attention to antimutagenic effect of 4,5-di-caffeoylquinic acid and 3,4,5-tri-caffeoylquinic acid against mutations induced by several chemical substances on the same bacterial strain; Trp-P-1, Trp-P-2 (3-Amino-1-methyl-5H-pyrido [4,3-b] indole) and 2-amino-3-methylimidazo [4,5-f] quinoline are found among these substances.

Cultivar/Variety	Identified/quantified compounds	Organ	Bioactivity	Reference
Multiple varieties	Chlorogenic acid; caffeic acid; 3,4-di-O-caffeoylquinic acid; 3,5-di-O-caffeoylquinic acid; 4,5-di-O-caffeoylquinic acid; 3,4,5-tri-O-caffeoylquinic acid	Leaves	Antimutagenic	Yoshimoto *et al.*, 2002
Multiple varieties	Chlorogenic acid; caffeic acid; 3,4-di-O-caffeoylquinic acid; 3,5-di-O-caffeoylquinic acid; 4,5-di-O-caffeoylquinic acid; 3,4,5-tri-O-caffeoylquinic acid	Leaves	No evaluated	Islam *et al*., 2002
Cv. Beniazuma (purple peel/yellow flesh)	β-D-fructofuranosyl-6-O-caffeoyl-α-D-glucopyranoside; 5-O-caffeoylquinic acid; caffeic acid; 3,5-di-O-caffeoylquinic acid; 4,5-di-O-caffeoylquinic acid; 3,4-di-O-caffeoylquinic	Roots	No evaluated	Takenaka *et al.*, 2006
Multiple varieties	Chlorogenic acid; caffeic acid; 3,4-di-O-caffeoylquinic acid; 3,5-di-O-caffeoylquinic acid; 4,5-di-O-caffeoylquinic acid; 3,4,5-tri-O-caffeoylquinic acid	Leaves	Antiradical (antioxidant), Antimutagenic	Islam *et al*., 2009
Whatley/Loretan (TU-155)	Chlorogenic acid; caffeic acid; quinic acid; 3,4-di-O-caffeoylquinic acid; 3,5-di-O-caffeoylquinic acid; 4,5-di-O-caffeoylquinic acid.	Leaves	Antiproliferative; antitumoral	Gundala *et al.*, 2013
Not indicated	Flavonoids; flavonols; anthocyanidins (cyanidin; malvidin)	Leaves	Antioxidant	Chao *et al*., 2014
Yuzi No. 7; Ximeng No. 1	Caffeic acid; 3-caffeoylquinic acid; 4-caffeoylquinic acid; 5-caffeoylquinic acid; 3,4-di-O-caffeoylquinic acid; 3,5-di-O-caffeoylquinic acid; 4,5-di-O-caffeoylquinic acid; 3,4,5-tri-O-caffeoylquinic acid	Leaves	Antioxidant	Xi *et al*., 2015
O´Henry (white), Beauregard (orange), 414-purple (purple)	*trans*-caffeic acid; 3-caffeoylquinic acid; caffeoylquinic acid isomers	Roots (peel, flesh)	No evaluated	Musilová *et al.*, 2017
Red and white	Total phenols; total flavonoids	Roots (peel, flesh)	Antiproliferative; antioxidant; antibacterial	Naz *et al*., 2017
cv. Bophelo (orange flesh)	Caffeic acid; catechin; hyperoside; isovanillic acid; kaempferol; protocatechuic acid; quercetin; rutin; vanillic acid	Leaves - roots	Antidiabetic	Ayeleso *et al.*, 2018
Not indicated (multiple accessions)	Chlorogenic acid; 4,5-di-O-caffeoylquinic acid; 3,4,5-tri-O-caffeoylquinic acid	Leaves	Antimutagenic	Islam, 2019

White (red peel), yellow	No evaluated	Roots (peel) – Ag nanoparticles	Cytotoxic; antioxidant; antibacterial; antidiabetic	Das *et al*., 2019
White, yellow, orange, purple	Chlorogenic acid; caffeic acid; syringic acid; cumaric acid; ferulic acid; trans-ferulic acid; isoquercetin; benzoic acid; isorhamnetin; hyperoside; catechin; epicatechin; coumarin; rutin hydrate	Roots	Antioxidant; antiproliferative	Sun *et al*., 2019

Table No. 1
Phenolic compounds identified or quantified in sweet potato extracts and their evaluated bioactivity

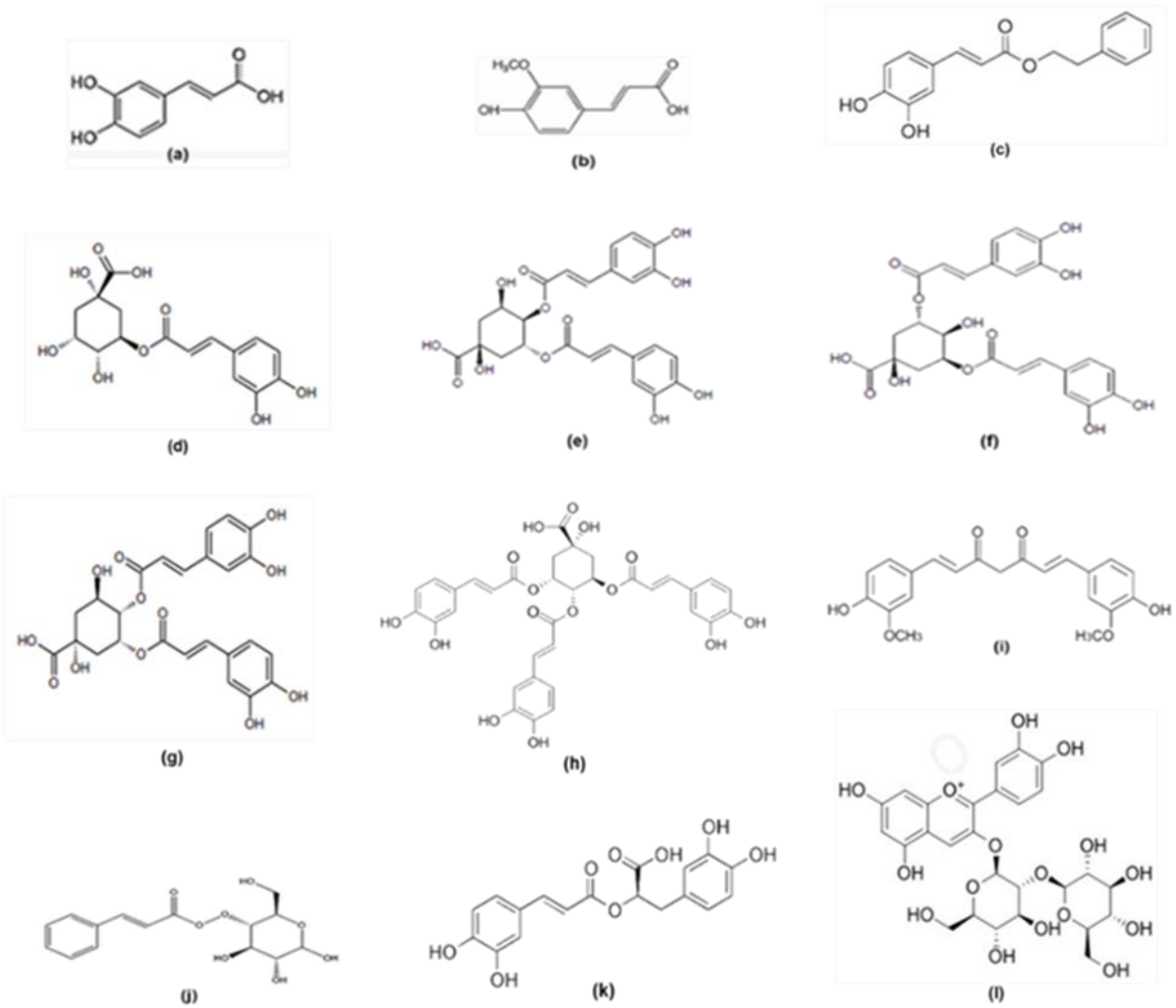

Figure No. 8
Main phenolic compounds identified in sweet potato and some derivatives. a) caffeic acid, b) ferulic acid, c) caffeic acid phenyl ester (CAPE), d) chlorogenic acid (3-caffeoylquinic acid), e) 3,4-dicapheoylquinic acid, f) 3,5-dicafeoylquinic acid, g) 4,5-dicapheoylquinic acid, h) 3,4,5-tricapheoylquinic acid, i) Curcumin, j) cinnamic acid glycosylate, k) rosmarinic acid, l) Cyanidin 3-soforosid

On the other hand, Konczak *et al.* (2003a), evaluated antioxidant, antimutagenic (induced by Trp-P-1) and antiproliferative (on HL-60 cell line [leukemia]) activities of aqueous extracts rich in anthocyanins obtained from roots and cells in suspension of a purple variety of sweet potato (cv. Ayamurasaki) with positive results in all cases, and concluding that bioactivity is dose dependent and is due to anthocyanins concentration in extracts. However, these results must be validated using *in vivo* systems, taking into account that works such as those by Celep *et al.* (2018) and Dabulici *et al.* (2020) prove that some bioactive substances (specifically phenolic acids) are poorly assimilated after gastrointestinal processes. An advance in this regard was made by Zhao *et al.* (2013), who corroborated antioxidant, hypoglycemic and antitumor effects of sweet potato extracts rich in anthocyanins when administered to mice. In the aforementioned work, cell line S180 (anal sarcoma) was evaluated and it was proven that anthocyanins-rich extract inhibited tumor growth by 68% at a dose of 1,000 $mgKg^{-1}$.

Although existing information shows that there are significant differences between sweet potato varieties and their polyphenol content and bioactivity, besides a correlation among them (Islam *et al*., 2002; Nagai *et al*., 2011) (Table No. 1), dependence among these variables cannot be established *a priori*. Naz *et al.* (2017) found no correspondence between extracts with the highest phenolic content (polyphenols and total flavonoids) and their antioxidant activity; likewise they did not find any correspondence between the latter and antiproliferative effect on immortalized MDBK (Madin-Darby bovine kidney) cells.

Similar results to previous ones were obtained with silver nanoparticles synthesized with extracts of tuberous root peel of sweet potato for the varieties "Red skin Korean" (Ib1) and "Korean pumpkin" (Ib2). In addition to demonstrating the bioactivity of said particles as a consequence of their basic composition (Ag), a differential and uncorrelated response was evidenced between antioxidant activity and antiproliferative activity on cells of HepG2 line. Thus, while Ib2 nanoparticles exhibited greater antioxidant potential, Ib1 nanoparticles showed greater antiproliferative activity; however, the authors have the idea that both were extremely toxic for the aforementioned cell line at concentrations of 1,000 μgmL^{-1}, decreasing cell viability by 40% (Das *et al*., 2019).

Available information shows that sweet potato extracts bioactivity is determined by individual compounds extracted, their concentrations, and relative proportions, giving way to either synergism or antagonism. Karna *et al*. (2011) and Gundala *et al*. (2013), found that fractionation of sweet potato crude extracts improved their bioactivity (up to 100 times more in fraction with the highest antiproliferative activity), but also they noted that sub-fractionation decreased it. Similarly, synergistic effect among extract constituents in relation to proliferation in a prostate cancer cell line inhibition using both *in vitro* and *in vivo* models, was demonstrated.

The bibliographic review carried out shows phenolic acids have not received as much attention as anticancer agents until recent years (Anantharaju *et al*., 2016; Kumar & Goel, 2019; Abotaleb *et al*., 2020), perhaps due to the fact that they are not present in high concentrations in most vegetables. However, it should be noted that these acids may be the most representative bioactive compounds in various species, as stated by Fraisse *et al.* (2011), and Rashmi & Negi (2020). Information about phenolic acids bioactivity is scattered and focused on only a few compounds (Ozturk *et al*., 2012; Damasceno *et al*., 2017; Kabała *et al*., 2017; Tang *et al*., 2017; Hernandes *et a*l., 2020; Jakubczyk *et al*., 2020), leaving an important gap in bioprospecting of these substances.

It is apparent that Islam *et al*. (2002), isolated caffeoylquinic acid and its derivatives (together) from sweet potato leaves for first time; later Islam *et al*. (2009), indicated that lack of information about physiological activity of these substances (and therefore about their bioactivity) is due to that they had not been isolated also together from a particular plant. Anticancerous effects of caffeic acid and its derivatives have been recognized and its bioactivity has been associated with O-hydroxyl group presence in catechol ring; the more caffeoyl groups these molecules have, the greater their effectiveness (Yoshimoto *et al*., 2002; Islam, 2019).

Lin *et al*. (2012) and Min *et al.* (2018) confirmed caffeic acid with placlitaxel synergism in proliferation control of A549 and H1299 cell lines (lung cancer) as well as in tumor progression through apoptosis and cell cycle arrest (phase G1) using both *in vitro* and *in vivo* models, this effect was differentially expressed whitout affecting normal cells. These results were related to increase in caspase activity after caffeic acid application, in addition to modulation of downstream targets under

NF-kB transcription factor (survivin and Blc-2). In this way elucidation of mechanisms associated with its bioactivity is improving. Several mechanisms of action of caffeic acid and its effects against various types of cancer (cervical carcinoma, ovarian carcinoma and fibrosarcoma) are mentioned in the works cited.

Kabała *et al*. (2017), evaluated caffeic acid bioactivity and caffeic acid phenethyl ester (CAPE), at 24 and 48 h of exposure using MDA-MB-231 cell line, and found that although caffeic acid affects cell viability to some degree (approximately 80% viable cells at [100 µM] regardless of exposure time), CAPE has a much higher cytotoxic effect (5.6% viable cells at [100 µM] with 48h of exposure), higher proapoptotic activity (24.85% live cells at [100 µM] with 48h of exposure), and is more efficient to stop cell cycle (S phase). CAPE bioactivity was associated with NF-kB specific inhibition, which is necessary for transition from epithelial to mesenchymal tissue and metastasis (Kabała *et al*., 2017) and results obtained by Kabała *et al.* (2018) using MCF-7 cell line, led to conclude that CAPE can also act on FOXF2, while caffeic acid acts on MCP-1 in this cell line.

Increase in phenolic compounds with activity against the MCF-7 and MDA-MB-231 lines (breast cancer) concentration was achieved via elicitation in sweet potato plants by Ghasemzadeh *et al*. (2016); these compounds comprise various phenolic acids and flavonoids such as quercetin, myricetin, caffeic acid, and two derivatives of the latter (3,5-dicafeoylquinic and 4,5-dicafeoylquinic acids).

It was shown that sweet potato foliar extracts rich in polyphenols inhibit growth and induce apoptosis in cell cultures and *in vivo* xenographic models of prostate cancer; according to this it can be stated that quinic and chlorogenic acids have to do with this effect, based on their relative concentration in the most active fraction (concentration 2.6 and 3.6 times higher, respectively, compared to other polyphenols) (Gundala *et al*., 2013). On the other hand, Naz *et al*. (2017) found that only sweet potato peel ethanolic extracts belonging to a white variety showed a perceptible antiproliferative activity (50 mg/mL) wich is much lower than that of paclitaxel; then they conclude that the evaluated extracts didn't have promising bioactivity, this also shows that type of solvent used influences extracts bioactivity, taking into account compounds that are extracted and their proportion.

Anticancer effect of a glycoprotein extracted from sweet potato (SPG-56) has recently been documented; this glycoprotein was tested with *in vitro* and *in vivo* models on HCT-116 (colon cancer) and MCF-7 (breast cancer) tumor lines, showing antiproliferative and antimetastatic activity and reduced tumors size in BALB/c nude mice (Wang *et al*., 2017b; Li *et al*., 2019), so participation of other kinds of substances in sweet potato bioactivity should not be underestimated and constitutes a research field that should be thoroughly explored.

Sweet potato in vitro culture and its potential in polyphenols production. Advantages of tissue culture in phenolic compounds obtaining

Potential of plant tissue culture in metabolites of interest production has gained importance several decades ago and growing demand for products rich in polyphenols has led to conducting many investigations aimed at improving elicitation conditions using *in vitro* systems; much of the above is in response to need to produce metabolites at an industrial level. With help of *in vitro* culture, possibility of manipulating biosynthetic pathways of plant cells is exploited by controlling culture conditions, based on the fact that cells and tissues have metabolic profiles similar to whole plant (even if cells are undifferentiated). Secondary metabolites production from cultured tissues is environmentally friendlier and therefore more sustainable, especially in slow-growing plants where production of certain substances is restricted to a certain phenological stage (Konczak *et al*., 2003a; Wang *et al*., 2017a; Chandran *et al*., 2020; Elateeq *et al*., 2020).

Although polyphenols production can be induced in plants, isolated organs, and callus grown in semisolid medium (Simões *et al*., 2012), cell suspensions are more advantageous since they can be initiated from small tissue portions and, once established, cells multiplication allows obtaining a large amount of new tissue, which in turn can be directed to produce metabolites of interest (Wang *et al*., 2017a; Chandran *et al*., 2020; Sánchez *et al*., 2020a), even in amounts greater than those contained in whole plant (Babich *et al*., 2020). Since a small amount of starting material is required added to the possibility of plant tissues reproducing in laboratory, without taking care of climatic variables, could reduce pressure on wild species (Espinosa *et al*., 2018). In this way the establishment of cultures in field for this purpose would be unnecessary, an other

item such as those regarding food security of populations would not be negatively affected.

There are studies where the growth dynamics of cell suspensions of sweet potato in presence of 2,4-dichlorophenoxyacetic acid (2,4-D) has been evaluated by establishing growth curves, which prove that the optimal concentration to rapidly increase cell volume in culture using this plant growth regulator is 2.26 µM (0.5 $mgL^{-1)}$ (González *et al*., 2011; Guevara *et al*., 2012). However, handling of such culture systems from sweet potato tissues has been done for several decades (Plata *et al*., 2003; Konczak *et al*., 2003a; Konczak *et al*., 2003b) and anthocyanins and phenolic acids production within them has been achieved with higher concentrations of this growth regulator and with variations of growing conditions (Konczak *et al*., 2005).

Chemical elicitation of polyphenols in cultured plant tissues

Regarding *in vitro* polyphenols production, a wide variety of species as well as of elicitors (physical, chemical, hormonal, biological, and in combination) have been evaluated; it has been found that even same phenolic compounds can act as such (Dias *et al*., 2016; Chandran *et al*., 2020). However, specific compounds production is still difficult due to the complexity associated with both metabolic pathways and extraction methods. Furthermore, culture age and processes involved in cell differentiation can change phytochemical profile of extracts; consequently, studies pointing at this direction are missing (Dias *et al*., 2016; Wang *et al*., 2017a).

Aminoacids (hydrolyzed casein, proline, phenylalanine), plant growth regulators, polyethylene glycol, unsaturated fatty acids, heavy metals or a mixture of several of these substances have been used in chemical elicitation of polyphenols (even in combination with other types of elicitors) (Naik & Al-Khayri, 2016; Thakur *et al*., 2018). Dias *et al*. (2016) make a list of some chemical elicitors used for phenolic *in vitro* production and the corresponding elicited species. However, it is believed that compounds of a hormonal nature induce an increase to a greater degree in phenolic compounds content in cultured tissues due to their capacity to regulate expression of downstream genes (Wang *et al*., 2017a). Table No. 2 shows some pieces of research where phenolic compounds production was induced by use of chemical elicitors.

Methyl jasmonate (MeJA) and salicylic acid (SA) are signaling molecules produced by the plant in response to different types of stress (both biotic and abiotic), modulating various metabolic pathways that increase gene expression that lead to phenols production (Złotek *et al*., 2016); these compounds have been commonly used as exogenous elicitors both in plants and in cultured tissues (Wang *et al*., 2017a). Although eliciting action of these compounds is not questioned, it should be noted that there are discrepancies regarding their classification, as can be seen in the bibliographic studies made by Dias *et al*. (2016), (abiotic/chemical), Naik & Al-Khayri (2016) (abiotic/hormonal), and Thakur *et al*. (2018) (biotic/hormonal). Considering that both compounds are applied exogenously and as pure agents using *in vitro* biological systems for elicitation purposes (Sánchez *et al*., 2020a), they will be considered abiotic/chemical for purposes of present review.

Application efficiency of SA, MeJA, and abscisic acid in polyphenols with antioxidant and anticancerous activity production in sweet potato plants was evaluated by Ghasemzadeh *et al.* (2016), with positive results; it was found that the first two compounds are more efficient as they can be emulated using *in vitro* cultures. A number of studies about phenolic compounds obtention in sweet potato cell suspensions involve phenolic acids production (Dias *et al*., 2016); however, anthocyanins obtention has also been achieved by elicitation with MeJA and *p*-coumaric acid (Plata *et al*., 2003; Konczak *et al*., 2003b).

Some publications relate phenolic compounds production from cultured plant tissues with presence of SA in culture medium (Akula & Ravishankar, 2011), but its effect has been found to be lower than that of MeJA (Mendoza *et al*., 2018). However, Riedel *et al*. (2012), found that jasmonic acid (JA), SA, ethephon, phenylalanine, and shikimic acid increased phenolic acids concentration and resveratrol derivatives in *Vitis vinifera* cell suspensions; there were no statistical differences between induction with JA or SA, but there were differences between induction with these and induction with other elicitors.

Species	Elicitor	Elicited compounds	Reference
Salvia officinalis	Sucrose (5%); phenylalanine	Rosmarinic acid	Hippolyte *et al.*, 1992
Vitis vinifera	Modification of mineral salts and sucrose concentration in the medium	Anthocyanins; tannins; catechins	Decendit & Mérillon, 1996
Ipomoea batatas	MeJA; *p*-coumaric acid	Anthocyanins (powered by light)	Plata *et al.*, 2003
Ipomoea batatas	MS medium + 1,0 mgL^{-1} 2,4-D; MS medium modified (9,4 mM KNO_3, without NH_4NO_3, 5% sucrosa; no growth regulators)	Anthocyanins	Konczak *et al.*, 2003a
Fragaria ananassa	Phenylalanine	Anthocyanins	Edahiro *et al.*, 2005
Lavandula vera	Vanadyl sulfate	Rosmarinic acid	Georgiev *et al*., 2006
Salvia miltiorrhiza	SA	caffeic acid; salvianolic acid B	Dong *et al*., 2010
Vitis vinifera	JA; SA; ethephone; phenylalanine; shicimic acid	vanillic acid; caffeic acid; chlorogenic acid; 3-O-glucosylresveratrol; 4-(3, 5-dihydroxyphenyl)-phenol; cinnamic acid	Riedel *et al*., 2012
Eryngium planum	MeJA; Sucrose (5%); yeast extract	Caffeic acid; rosmarinic acid; chlorogenic acid	Kikowska *et al.*, 2015
Nardostachys jatamansi	MeJA	Flavonoids, tannins, phenolic acids	Rawat *et al.*, 2019
Orostachys cartilaginous	SA	Flavonoids y total phenolics (quercetin; kaempferide; epicatechin gallate; quercetin-3-O-glucose; kaempferol-3-rutinoside	Wen *et al*., 2019
Ocimum basilicum	yeast extract; $AgNO_3$; $CdCl_2$	Flavonoids y total phenolics (Chicoric acid; rosmarinic acid; rutin; isoquercetin)	Açıkgöz, 2020
Sequoia sempervirens	Phenylalanine; $AgNO_3$ (alone or in combination with UV radiation)	Luteolin; quercetin; kaempferol; apigenin	El-Hawary *et al.*, 2019
Levisticum officinale Koch	JA; yeast extract	Protocatechuic acid; hydroxybenzoic acid; siringic acid; vanillic acid; sinapic acid; salicylic acid; caffeic acid	Jakubczyk *et al*., 2020
Capparis spinosa	SA; MeJA	Rutin	Kianersi *et al.*, 2020

Table No. 2
Some chemical elicitors used to obtain phenolic compounds employing *in vitro* culture systems

Finally, it should be mentioned that due to stressful nature of abiotic elicitors, cultured tissues tolerate them at relatively low concentrations and respond by producing phenols, but starting from certain concentrations they can inhibit both production of these substances and gain of biomass in cell suspensions this was proved by Riedel *et al*. (2012) and Rawat *et al*. (2019) with JA and MeJA, respectively. In the same direction, Kianersi *et al*. (2020) reported positive effect on progressive gain of fresh mass in *Capparis spinosa* L. calli exposed to SA or MeJA up to concentrations of 100 mgL^{-1} and 10 µM (respectively); in the same way, they found that at higher concentrations of these elicitors fresh mass gain of calli was reduced, although it was still higher than that obtained in control treatment.

CONCLUSIONS AND PROSPECTS

Research aimed at obtaining bioactive phenolic compounds from sweet potato is a growing field all over the world and its production using *in vitro* culture systems has been projected in the last 30 years. Phenols produced from this species have high potential in cancer prevention and cancer treatment, this being related both to concentration of these substances and their relative proportions in extracts. Asian countries have produced a high variety of sweet potato genotypes and are known for enormous amount of information related to research in this field; on the contrary, in Central and South American countries information is not abundant and it is scattered.

Variation in polyphenols content evidenced among varieties or cultivars of sweet potato is reflected in their cell suspensions, and *in vitro* culture conditions as well as the type of elicitor to be used must be adjusted for each particular case. Correspondly, it will be necessary to know elicitation conditions of a large number of sweet potato genotypes that guarantee an increasingly efficient compounds of interest production with less environmental impact. Thus, industrialization of sweet potato as a source of substances with high bioactivity will require the making of a search for superior genotypes, with a greater impact in Latin American countries, as it is the place the species is from. In relation to the above, Colombia, Peru, and Ecuador are recognized for their wide diversity of sweet potato, as indicated by Rosero *et al*. (2019).

Sweet potato cultivation in Colombia would be favored due to diversity of agroclimatic conditions and soil types present in this country, making use of lands that due to their aridity do not allow growing of other crops. This added to relatively low production costs would allow inclusion of this resource in official development plans, within framework of bioeconomy. In this sense, the Colombian organization that has devoted most effort to sweet potato research is Agrosavia (formerly Corpoica), both individually or in association with others. These efforts have an evident agronomic interest and are reflected in the works written by Morales *et al.* (2017), Pérez & Sánchez (2017), Rosero *et al*. (2019), Rosero *et al*. (2020), Burbano *et al.* (2020), Sánchez *et al*. (2020b) and Támara *et al*. (2020).

There are also works done in universities of Córdoba and Sucre departments (Colombia) about cultivation and industrial use of sweet potato, as evidenced in the works written by Arrázola *et al*. (2016), Andrade *et al*. (2018), Ariza *et al*. (2019), Jiménez *et al*. (2019) and Arrázola *et al*. (2020). In addition, there is a research done by Guevara *et al*. (2012), whose results provide information on conditions for induction and proliferation callus from sweet potato leaf explants; this is a piece that could be used in subsequent biotechnological use of this plant. Unfortunately, there are no developments concerning to bioactivity evaluation, nor about isolation production of metabolites of interest from this species.

Although roots and leaves of sweet potato are good choices for obtaining polyphenols, gathering involves whole plant destruction and elicitation of these compounds in cell suspensions is more sustainable. Then it is possible to get rid of drawbacks associated with variable concentration of these substances in plants grown in field, considering at the same time their large-scale production. Further, uses of the plant leaves after tuberous roots gathering have not been evaluated.

Chemical elicitors are very efficient to modulate metabolic pathways that lead to phenolic acids production; jasmonates and SA use has shown promising results due to their hormonal nature. Additionally, ample list of biological activities attributed to sweet potato constitutes an opportunity to explore various research fields aimed at obtaining new drugs, which are less toxic to normal cells, and the possibility of applying more recent approaches such as those related to *in silico* studies.

Regarding medical, therapeutic polyphenols use, the fact that assimilation of a certain substance *in vivo* is required for exhibiting their bioactivity (Dabulici *et al*., 2020) must be taken into account.

Although *in vitro* studies offer advantages such as ease, speed, and relative low cost (Moleiro *et al*., 2017), response observed in this type of studies may differ from *in vivo* response, as a consequence of anatomical complexity and metabolic processes of animals (biotransformation, degradation by body itself or by associated gut microbiota, and poor or no absorption in gut) (Gonthier *et al*., 2003; Bilal-Hussain *et al*., 2019; Dabulici *et al*., 2020) thus bioactive compounds assimilation can vary among individuals, as indicated by Almeida *et al*. (2018).

Considering the above, preliminary positive results when analyzing an extract or a fraction must be fully validated, going all the way from purely chemical tests to preclinical trials. Furthermore, there is evidence of need to continue exploring development of vehicles that prevent or delay degradation phenolic compounds when administered (Vulić *et al*., 2019); combination with other technologies (probiotics and prebiotics use) would improve their assimilation (Vamanu & Gatea, 2020).

Finally, for bioactive substances production at an industrial level a number of items should be considered: laboratories and specialized personnel, cell suspensions potential loss, scale up processes, bioactivity differences of elicited compounds and, antagonistic effects that would exist among constituents in a same extract. These factors will determine the economic viability of a project of such a kind.

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