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Review article

Bioactive compounds as an alternative for the sugarcane industry: Towards an integrative approach

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ABSTRACT

Here, a comprehensive review of sugarcane industrialization and its relationship with bioactive compounds (BCs) detected in various products and by-products generated during its processing is presented. Furthermore, it is discussed how these compounds have revealed important antioxidant, antineoplastic, antidiabetic, and antimicrobial activities. From this bibliographic research highlights the significance of two types of BCs of natural origin (phenolic compounds (PCs) and terpenoids) and a group of compounds synthesized during industrial transformation processes (Maillard reaction products (MRPs)). It was found that most of the studies about the BCs from sugarcane have been conducted by identifying, isolating, and analyzing ones or a few compounds at a specific period, this being a conventional approach. However, given the complexity of the synthesis processes of all these BCs and the biological activities they can manifest in a specific biological context, novel approaches are needed to address these analyses holistically. To overcome this challenge, integrating massive and multiscale methods, such as omics sciences, seems necessary to enrich these studies. This work is intended to contribute to the state of the art that could support future research about the exploration, characterization, or evaluation of different bioactive molecules from sugarcane and its derivatives.

1. Introduction

One of the most important agricultural products at an industrial level is sugarcane. According to statistical data from the Food and Agriculture Organization of the United Nations (FAO), this crop has the highest production worldwide, with around 1.87 billion tons of harvested sugarcane in 2020 [1]. These high production volumes highlight the impact of this agroindustry, not only at the socio-economic level but also in an environmental context. From a circular economy perspective, some concerns have arisen related to sugar production, the generation of by-products and waste, and the sustainable development of the sugarcane industry [2–4]. Although sugarcane has been regarded as one of the most significant and efficient sources of biomass for biofuels production (sugar-based ethanol) and electricity co-generation (mainly from bagasse) [5], interestingly, the sugarcane cluster has been characterized by

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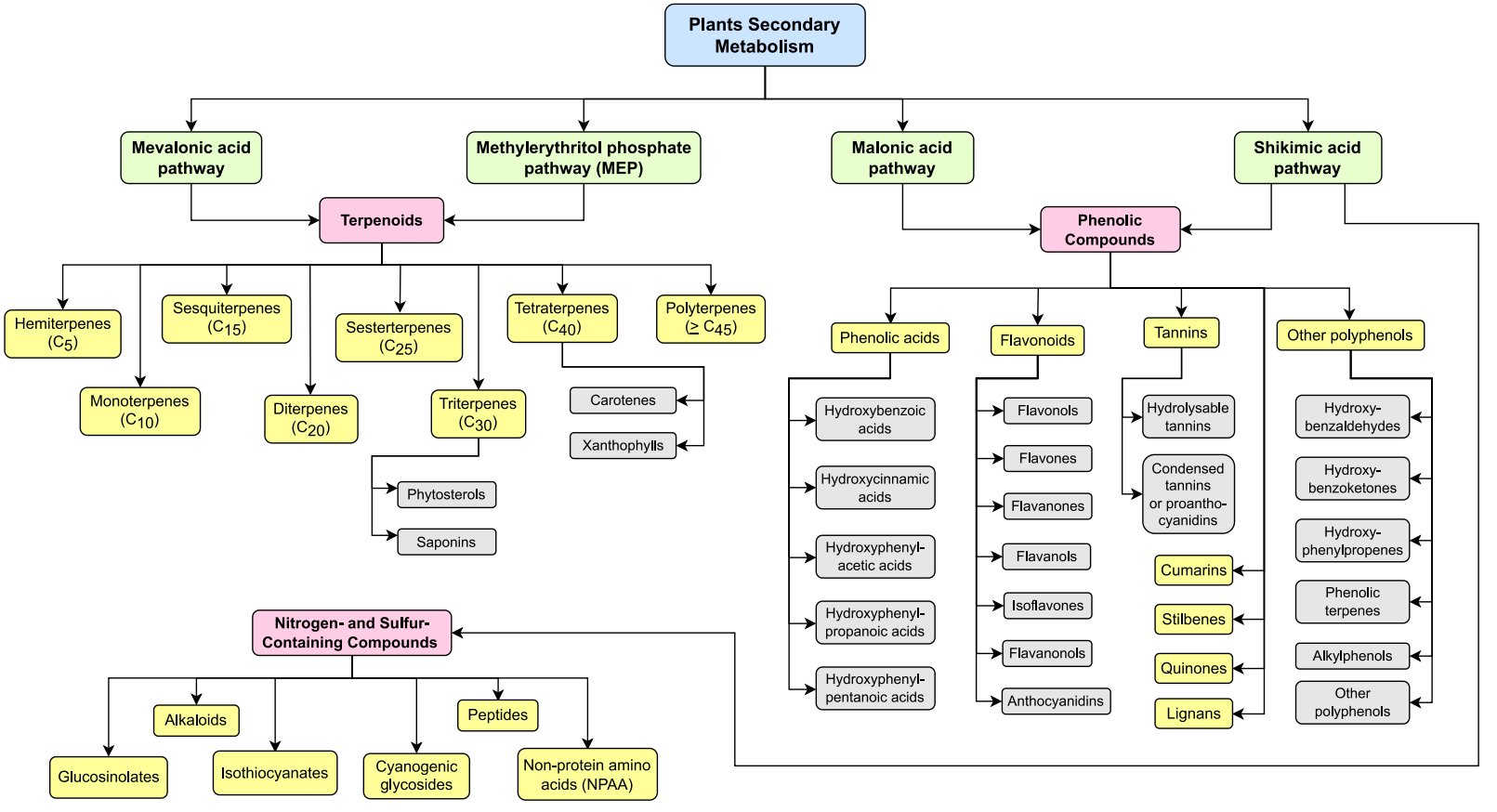

Fig. 1. Classification of secondary metabolites of plants. Image by the authors.

maintaining a constant search for alternatives that promote the integral use of the different resources of this agroindustry [2]. Therefore, the study and formulation of new strategies contribute to improving the productivity and sustainability of this sector. It also promotes greater diversification and added value of products derived from sugarcane. Under this perspective, there has been a growing interest in sugarcane products, by-products, and the whole plant, due to its potential as a source of bioactive compounds (BCs) [6].

Among the most studied BCs around sugarcane are phenolic compounds (PCs) and terpenoids. A wide variety of these two types of phytochemicals have been found in diverse sugarcane varieties throughout their different organs (Supplementary Material 1). In some cases, these compounds remain in several products and by-products obtained during their processing [7,8]. Another type of molecules that has shown potential as BCs are melanoidins, which are part of the so-called Maillard reaction products (MRPs). These compounds are synthesized during the industrialization processes of sugarcane due to the presence of both amino compounds and reducing sugars in the plant [9,10].

Conventionally, multiple procedures have been applied to identify bioactive molecules and explore their biological properties. Among the properties observed in different *in vitro* studies, antioxidant, antimicrobial, antidiabetic, and antiproliferative effects have been found [11,12]. Although these advances have prompted the study of BCs, their practical application and scaling to industrial levels have been restricted due to the use of traditional methodologies for their identification and evaluation, limiting the scope of the analysis to a few compounds at a time. To advance in future applications in various fields of general interest, it is necessary to complement conventional compound extraction and separation methodologies with massive exploration and identification techniques, such as multi-omics, which broaden the range of compounds to be studied [13]. Implementing methodological strategies under omics approaches could represent a great opportunity in various food or pharmacological applications, for example, for developing new nutraceutical products, functional foods, or even for the definition of a personalized diet for precision health [14].

This paper presents the results of an exhaustive and systematic review of the current scientific literature about the BCs found in sugarcane and its derivatives and their main biological activities. For this, different documents of academic and scientific nature were consulted, such as articles, book chapters, scientific reports, and doctoral theses published from 2000 to the present, through the Science Direct, Springer, Wiley Online Library, and Google Scholar databases. The following predefined set of keywords combined was used as search criteria: sugarcane, bioactive compounds, processing, by-products, waste, phenolic compounds, terpenoids,

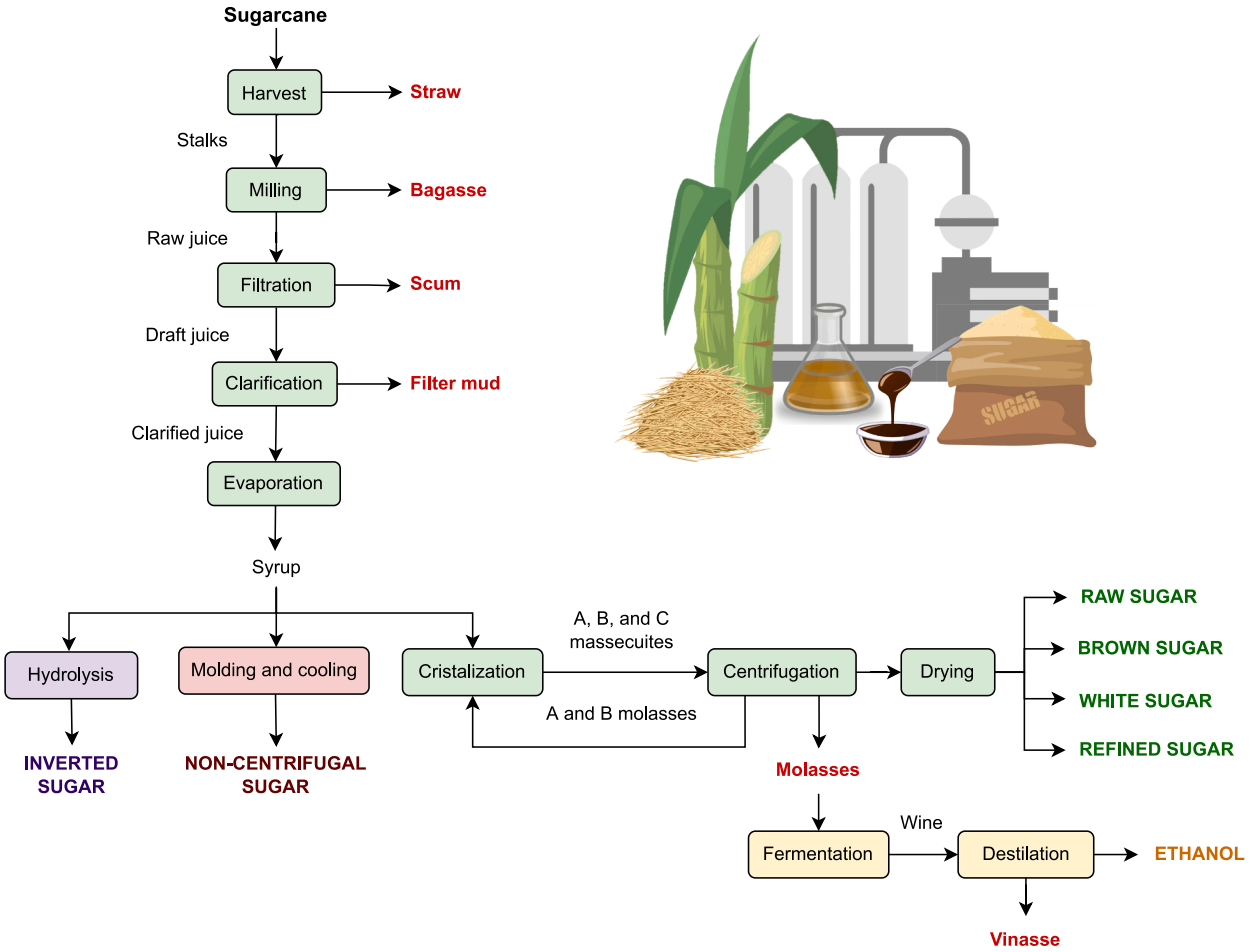

Fig. 2. Processing of sugarcane with products and by-products. Image by the authors.

melanoidins, and Maillard products. Certified scientific-technical sources, such as research centers, organizations, and associations, were consulted for specific data about the sugarcane industry. The main purpose of this paper is to contribute to the state of the art so that, beyond facilitating access to existing information, the current understanding of these topics is broadened, considering not only a traditional vision but also more holistic aspects such as those related to metabolomics approaches. This work is expected to encourage research in these fields, boosting sugarcane products, by-products, and wastes as promising sources of biologically active compounds.

2. Generalities about bioactive compounds

Although the definition of BCs is not yet unanimous in the scientific community, one of the most accepted establishes that they are natural or synthetic compounds capable of interacting with one or more components in living tissues and exerting a wide range of biological responses [4,15]. Its impact on the food industry represents a great interest due to the remarkable increase of studies about several compounds included in frequent-intake foods that demonstrate nutritive properties with relevant biological activity in the treatment and prevention of chronic diseases (*e.g.,* diabetes, hypertension, and cancer) [4,16,17]. A wide range of BCs has been identified that differ in structure and function depending on their origin. For plant-origin compounds, different biological activities have been associated with some chemical compounds synthesized during secondary metabolism. These metabolites, also called phytochemicals, play various non-nutritional roles in plants, for example, those related to their defense system against physico-chemical and biological agents (*e.g.*, ultraviolet radiation, oxidizing agents, microorganisms, parasites, predators, diseases, etc.) [18]. Besides, some of these secondary metabolites give plant products features such as color, flavor, and aroma, which are biologically related to the adaptation mechanisms of the environment but are also used industrially as quality attributes [17]. BCs of plant origin are classified according to their biosynthetic pathways and structure. Therefore, the main categories of secondary metabolites correspond to phenolic compounds (PCs), terpenoids, and nitrogen- and sulfur-containing compounds [19,20] (Fig. 1). By considering the structural diversity of phytochemicals, some subgroups or families of compounds share common characteristics important for the

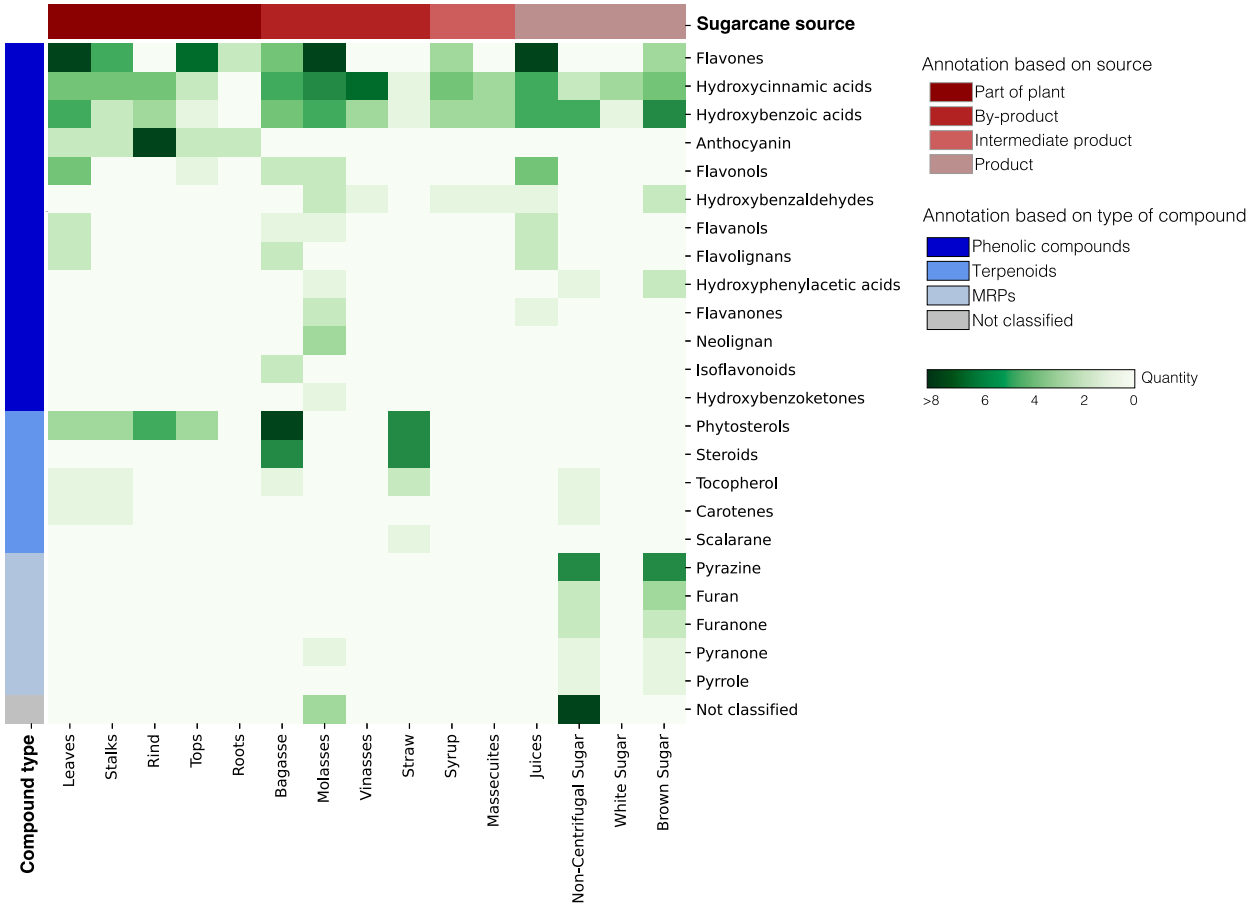

Fig. 3. Heatmap of quantitative report of BC found in sugarcane from bibliographic records (Supported by the supplementary Material 1). The class distribution for phenolic compounds, terpenoids, and MRPs (Blue scale) were compared with the distribution of the main subclasses of BCs in the sugarcane organs, products, and by-products (Red scale). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

processes of identification, quantification, extraction, and evaluation of biological activities [17–19,21,22].

3. Bioactive compounds from sugarcane and its derivatives

Sugarcane is economically important due to the multiple products and by-products generated from its processing (Fig. 2). Traditionally, industrial interest has focused on the stalks since it is there where sucrose accumulates. However, recent studies have shown that agro-industrial residues from different crops, including sugarcane, should be considered a renewable source of BCs with added value [4,6].

While BCs can be classified according to their source or chemical properties, in an industrial crop like sugarcane, it is possible to establish a more precise classification of phytochemicals based on their quantity in specific sources such as the different plant organs and the products and by-products obtained from its processing (Fig. 3). Herein, it has been evidenced how sugarcane industrialization processes could boost compound diversity in specific sources. However, it is feasible that the exploration of some typical compounds may overlap others with significant value but with lower concentrations per sample that could have been neglected in extraction processes, for example, some carotenes, flavones, or new compounds from the Maillard reaction (Supplementary Material 1). Next, a detailed bibliographical review of the BCs identified in sugarcane and derivatives, but with significant concentrations and biological activities, is presented.

3.1. Phytochemicals found in sugarcane

Sugarcane produces a wealth of BCs during its growth due to metabolic causes or in response to different biotic and abiotic factors. In fact, the study of gene expression patterns associated with the main biosynthetic pathways of the secondary metabolism of sugarcane indicates that during the development stages of specific tissues and the adaptive response to stress agents, the greater activation pathways are related to terpenoids and PCs biosynthesis [23]. Particularly, these two types of phytochemicals are distributed in distinct sugarcane organs, showing significant modulatory effects *in vitro* on one or several physiological functions as antimicrobial,

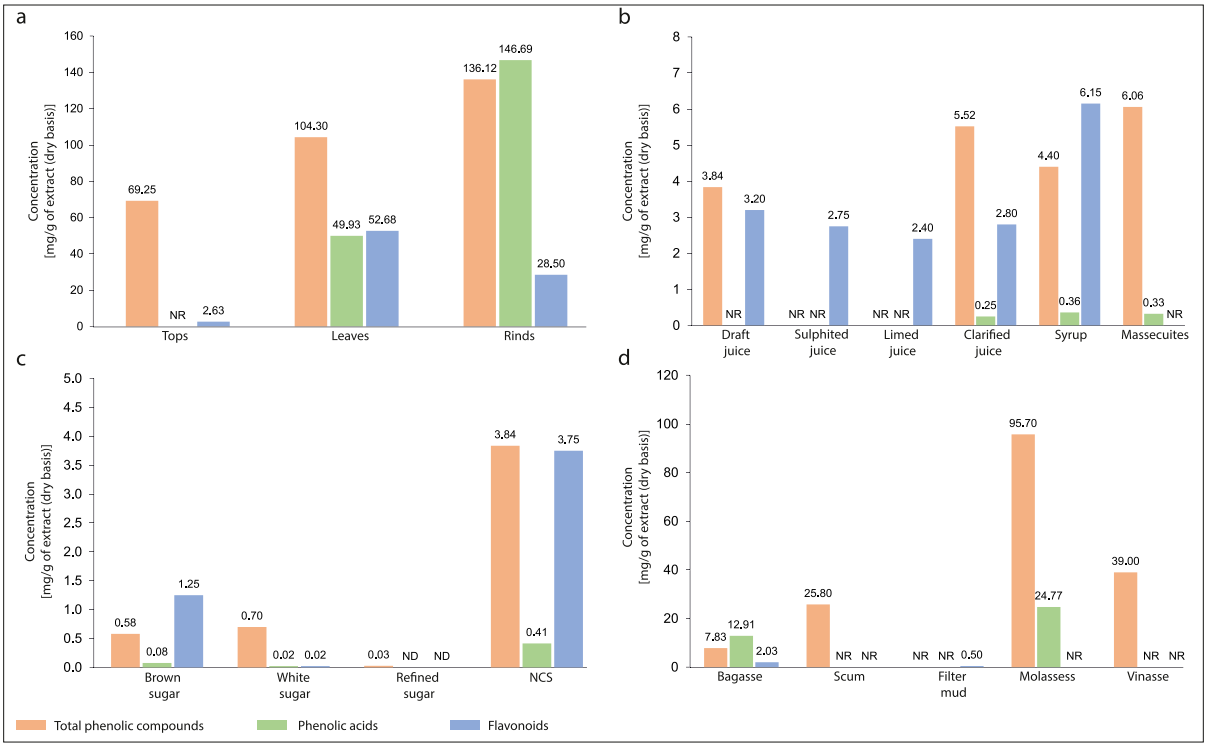

Fig. 4. Concentration of PCs found in sugarcane products and by-products. (a) Variations in different sugarcane organs (tops [25,26], leaves [107,108,111,114], and rind [32,34]). (b) Variations in different intermediate products generated during sugarcane processing (draft juice [45,152], sulphited juice [45], limed juice [45], clarified juice [8,45], syrup [8,60], and massecuites [8]). (c) Variations in different products of sugarcane processing (brown sugar [10,59,60], white sugar [8,59,60], refined sugar [59], and non-centrifugal sugar (NCS) [59,60]). (d) Variations in different by-products generated during sugarcane processing (bagasse [42,43], scum [47], filter mud [45], molasses [8,45,65,108], and vinasse [9]). NR: Data not reported. ND: Concentration not detected. Data used for bar charts correspond to the average values reported in the literature. There may be variations associated with the different methodologies used, as well as the raw materials analyzed. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

antidiabetic, anti-inflammatory, antiproliferative, antioxidant, and cytoprotective agents (Supplementary Material 1).

Sugarcane leaves, tops, and inflorescences constitute a by-product industrially known as straw that represents about 20% of the dry weight of the plant [24]. Several studies have evaluated the presence of biologically active secondary metabolites in sugarcane straw, mainly in leaves and tops (Fig. 4a). For example, eight PCs were identified in different extracts obtained from plant tops: caffeic acid, *cis*-p-hydroxycinnamic acid, quercetin, apigenin, albanin A, australone A, moracin M, and 5′-geranyl-5,7,2′,4′-tetrahydroxyflavone [25]. All these compounds directly correlated with antioxidant capacity and nitrite-scavenging *in vitro*. On the other hand, in Chinese cane, a commercial species from Asia, the identification of PCs was equally positive since significant quantities of several flavonoids were found, which were significantly higher in leaves and tops (3.85 and 2.63 mg of flavonoids/g of dry matter, respectively) compared to those reported in stalks (1.91 mg/g) [26]. Complementarily, several BCs in leaves have been validated in commercial sugarcane varieties, including phenolic acids, anthocyanins, flavanols, flavones, tannins, diterpenes, phytosterols, and tetraterpenes [27]. From that study, a phytochemical catalog of 56 metabolites from sugarcane leaves was proposed, grouped according to the content of flavones, phenolic acids, and glycosides. Another research evaluated secondary metabolites produced by wild-type and transgenic sugarcane plants grown in greenhouses [28,29]. Therein, similar concentrations were observed among some flavonoids found in both types of plants, such as tricin-4′-*O*-(erythro or threo guaiacylglyceryl) ether-7-*O*-glucopyranoside, tricin-4′-*O*-(erythro or threo guaiacylglyceryl) ether, diosmetin-8-*C*-glycoside, and diosmetin-8-*C*-glycosidearabinoside. Despite this, there were significant differences concerning the total flavonoid content since the transgenic samples showed values in some cases higher and, in others, lower than the control samples, which could indicate that the biosynthesis of flavonoids could be affected by the introduction of genes from other organisms into the sugarcane genetic material [28].

Regarding sugarcane stalks, several studies suggest that their rinds could be a good source of PC and terpenoids with important biological activities [30–35]. From this source, some phytosterols have been detected with a possible role in reducing total cholesterol levels in the blood [30], as well as various phenolic acids such as p-coumaric, gallic, chlorogenic, and ferulic; which correlate positively with free radical scavenging *in vitro* [31,32]. Additionally, some flavonoids have been found in sugarcane rinds, specifically, anthocyanins, which have exhibited antioxidant activities and inhibitory effects on the growth of some cancer cell lines [34,35]. Since stalks are the organ that receives the most industrial attention, the discussion about its importance as a source of BCs will be oriented by analyzing the products and the by-products generated from their processing (*i.e.,* juices and bagasse, respectively).

3.2. Phytochemicals found in sugarcane products and by-products

3.2.1. Stage 1: juicing extraction process

After harvesting, the sugarcane stalks go through a milling process, generating two output streams: one liquid stream as the main product and one solid fraction as waste material. This solid fraction, known as bagasse, is the main by-product of the sugarcane industry, as it corresponds to about 30% of the stalks weight [2,36]. Although this by-product has been widely used as raw material for energy generation and paper production [2,36,37], it has been explored as a remarkable source of flavonoids (0.381 mg/g) [28], being even comparable to some fruits known for their high concentration of these phytochemicals (*e.g.*, peaches - 0.237 mg/g [38] and tomatoes - 0.256 mg/g [39]). It has been proven that some PCs from sugarcane bagasse not only show a high antioxidant capacity but have also revealed interesting antimicrobial, antidiabetic, antiproliferative, and antifibrotic properties [12,40–43]. For this reason, this by-product could be considered a viable option to be used by both pharmaceutical and food-processing industries. On the other hand, although in fewer representative proportions, some terpenoids have been recognized in sugarcane bagasse, including tocopherols (α-tocopherol = 0.010 mg/g), phytosterols (sitosterol = 0.012 mg/g, campesterol = 0.009 mg/g, campestanol = 0.007 mg/g, stigmasterol = 0.006 mg/g, stigmastanol = 0.004 mg/g and 7-oxositosterol = 0.002 mg/g), and other triterpenoids (isoarborinol = 0.002 mg/g) [44].

The liquid stream from milling processes corresponds to a first raw juice with abundant residual bagasse fibrils in suspension. This suspended material, called scum, is removed by filtration to obtain an insoluble-solids-free juice known as draft juice [45,46]. Some studies have reported that scum can be considered as a suitable by-product for extracting BCs, since contents of around 25.8 mg of polyphenols/g of sample (on a dry matter basis) have been reported, and it presents a high association with antioxidant activities *in vitro* [47,48]. Concerning the raw juice, this is a turbid liquid with a marked coloration in different green-brown shades and serves as a substrate for the subsequent extraction of sucrose. These typical colors of the raw juices depend, among other factors, on different types of compounds of natural origin, including pigments and PCs [49,50]. There exist multiple phenolic-type BCs in raw juices, mainly phenolic acids and flavonoids, specifically flavones like apigenin, luteolin, and tricin and their glycosides [49,51–54]. Total flavonoids contents of 0.695 mg/mL of raw juice have been reported [28], which could compare to those from other beverages such as orange juice (0.200 mg/mL) [55] or black tea (0.830 mg/mL) [56], both highly valued for their antioxidant properties.

3.2.2. Stage 2: juice clarification process

Filtered raw juices, *i.e.,* the draft juices, undergo a clarification process, going through a series of phases that include the following treatments: sulphitation, liming, heating, and flocculation. From this process, a clear juice free of proteins, waxes, polysaccharides, color formers compounds, and high molecular weight compounds is obtained [10,45,47]. As waste material, a by-product called filter mud is generated, which represents an approximate production of 30 kg/ton of milled sugarcane and has traditionally been used as fertilizer in sugarcane crops [57]. According to the reported literature, when analyzing each product generated during these stages (*i.e.,* sulphited juice, limed juice, clarified juice, and filter mud), a notable presence of flavonoids was found that vary as the clarification process progresses [45]. Among these variations, it highlights the reduction in the flavonoid content between the intermediate juices (Fig. 4b). In fact, it was reported that some BCs from sugarcane stalks could be adversely affected by changes in pH and temperature

induced by the factory processes, more specifically those involved in clarification [45]. Despite this, given the marked difference between flavonoid concentrations of clarified juice (2.80 mg/g) and filter mud (0.50 mg/g) [45] (Fig. 4b and d), it can be observed a high retention degree of these compounds in the juice. About this point, in a previous study, the phytochemicals present in clarified sugarcane juices were characterized, confirming that these are a good source of flavonoids, but also of phenolic acids [8]. On the other hand, although the concentration of flavonoids detected in filter mud is low, it would be interesting to explore other alternatives for the industrial valorization of this by-product as an eventual source of biologically active compounds.

3.2.3. Stage 3: juice concentration and sugar obtaining processes

Considering that clarified juices have a soluble solids content of approximately 15% and that the greatest industrial interest has been oriented towards maximizing sucrose extraction, it is necessary to eliminate as much water as possible from these juices through a multiple-effect evaporation process. From this stage, a dark syrup about 60–65 °Brix is produced, which concentrates sugars and other color-generating molecules like PCs. To date, flavonoids and phenolic acids have been detected in syrup at higher concentrations than those registered in clarified juices [10,53] (Fig. 4b).

At this stage in the sugarcane transformation process, it is possible to use the syrup to obtain two types of sugar of commercial interest: inverted sugar and non-centrifugal sugar (NCS). Regarding the potential of these two products as a source of BCs, it has been highlighted that NCS presents a composition rich in amino acids, vitamins, and PCs, the latter in quantities between 0.4149 and 3.837 mg/g of sample [58–61] (Fig. 4c). The presence of these BCs has been shown to be closely related to antioxidant, antimicrobial, and protective activities against DNA damage [58,61–64]. Conversely, as far as inverted sugar is concerned, no data about the presence of BCs in this product have been reported. Therefore, this is an open topic that would be worth deepening.

Meanwhile, sugar, the final product of the manufacturing process, is obtained when syrup is conducted through a series of vacuum crystallization pans of three continuous stations to induce the nucleation and growth of sugar crystals [47]. In each station, a mixture of supersaturated syrup and sucrose crystals, called massecuite, is formed, which classifies according to its purity in A, B, and C massecuite [10,46,47]. These massecuites are centrifuged to separate the crystals, generating one output for each station: A, B, and C molasses. A and B molasses are fed back into crystallization pans to maximize the sucrose extraction. C molasses, or just called molasses, is a complex mixture of non-crystallizable syrups that, although it does not offer a higher recovery of sucrose, presents a composition rich in phenolic acids, flavonoids, and lignans which have been found in concentrations that far exceed those reported in massecuites, syrup, and clarified juices [10,51,53,65–70] (Fig. 4b and d). Pharmaceutical and food industries have shown great interest in molasses since they have become a highly valued by-product, not only because of its traditional use for ethanol production [2] but also by their highly appreciated activities as antibacterial [69], antidiabetic [51,68,71], and antioxidant agents [7,51,65,66,70], which are associated with the presence of BCs.

Finally, the sugar crystals separated by centrifugation are dried; from them, it is possible to obtain different types of sugar, such as raw sugar, brown sugar, white sugar, and refined sugar [10,47]. According to the literature, there has been a negligible presence, and in some cases, a total absence of BCs found in some types of sugars [8,45,59,60]. Notably, brown sugar conserves some flavonoids and phenolic acids that, despite appearing in relatively low concentrations (Fig. 4c), confer interesting qualities to be considered as a product with potential bioactive properties [10,53,59,60].

3.2.4. Stage 4: bio-ethanol production process

One process derived from the sugarcane transformation is carried out by refineries that use this plant or its by-products to produce biofuels (first- or second-generation ethanol). As a result of the distillation of wines produced by yeasts during fermentation, an effluent known as vinasse is generated. Traditionally, vinasses have been known as industrial waste with high polluting potential due to their low pH and high biochemical oxygen demand [7,72,73] However, it has been reported that this effluent represents an important source of PCs with demonstrated bioactive properties like antioxidant and antimicrobial agents [7,74,75]. In fact, vinasses have been found to have a total phenolic content between 28 and 39 mg/g dry sample (Fig. 4d), with a remarkable presence of several phenolic acids such as p-hydroxybenzoic, syringic, ferulic, p-coumaric, and vanillic acid [9]. These findings translate into an outstanding opportunity for vinasses as by-product due to its potential as a significant source of new or uncharacterized BCs.

3.3. Bioactive compounds formed during the manufacturing process

Although most of the BCs found in various products and by-products derived from sugarcane come directly from the secondary metabolism of the plant, some others may be formed during the manufacturing process, for example, because of changes in temperature, pH, or by the interaction between the different components in sugarcane. One of the best-known cases corresponds to the generation of Maillard reaction products (MRPs). MRPs arise from the reaction between free amino groups and carbonyl groups, with the intermediation of high temperatures involved throughout the manufacturing processes [76,77]. Particularly during sugarcane processing, MRPs can be synthesized in processes that involve temperature increases, *e.g.,* during juices clarification and evaporation. These compounds not only contribute to the typical development of flavors, aromas, and brown colors typical of sugarcane products but also present antioxidant and anti-inflammatory activities that add to the effects exerted by PCs [8,10,59,60,62]. Considering this evidence, results reported by different researchers regarding the total phenols content could be biased since the most used test for this estimation, *i.e.*, the Folin-Ciocalteu test, provides a measure of all those easily oxidable compounds under the established experimental conditions. These characteristics make this test not specific for PCs, so MRPs are also detected, leading to overestimation problems [8,10,59,60]. To overcome these problems and characterize, more specifically, the BCs present in a sample, it is necessary to perform complementary tests based on chromatography, spectroscopy, or spectrometry methods. Due to the application of this kind of

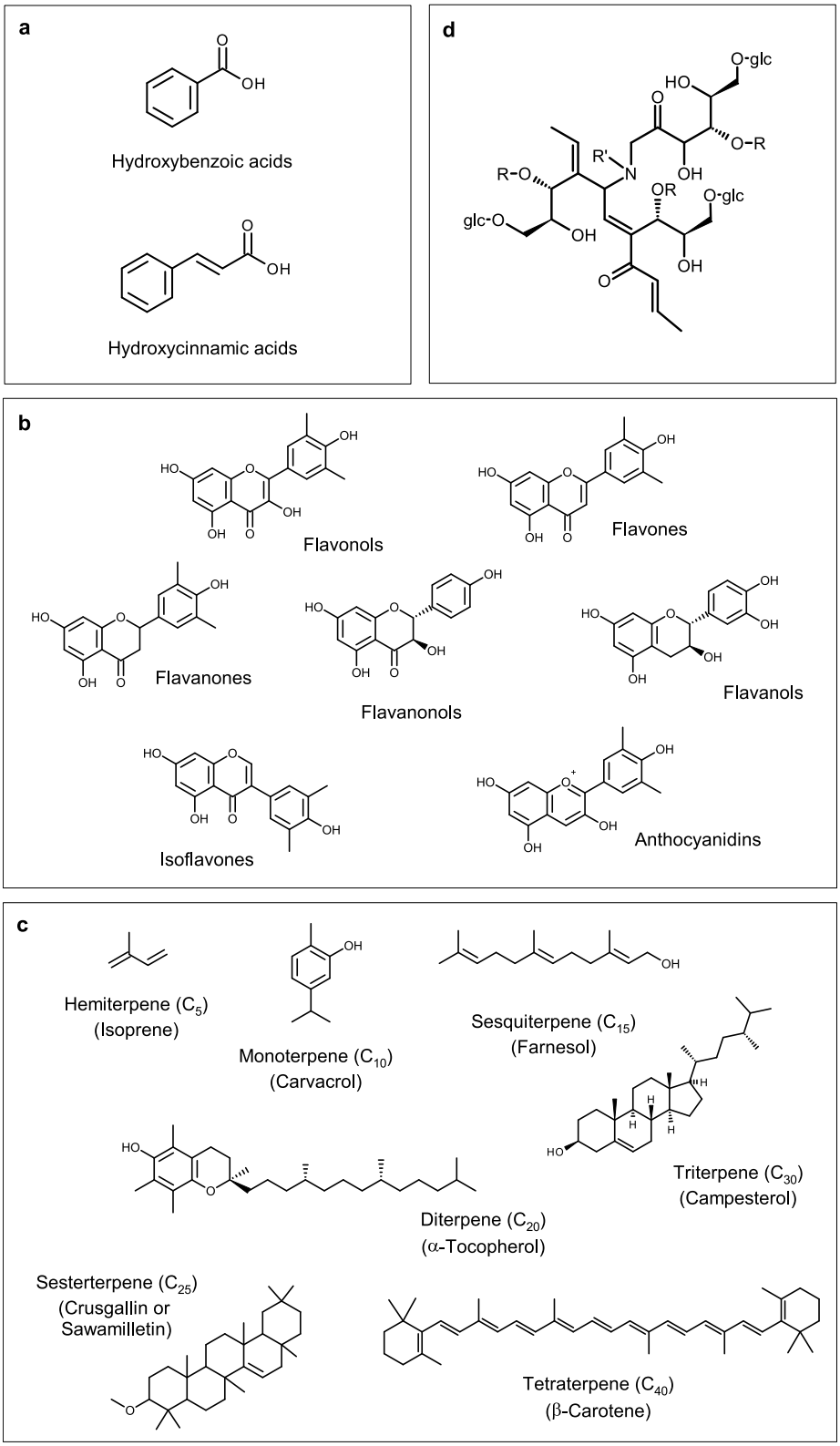

Fig. 5. Generic molecular structure of some BCs: (a) Phenolic acids. (b) Flavonoids, (c) Terpenoids, and (d) Melanoidin formed from a sugar-amino acid model system, where R represents the location of a hydrogen atom or carbohydrates, and R′ represents the side chains of amino acids [87–89] (Reprinted with permission from Elsevier). Drawings made with ChemSketch Freeware 2021.2.1.

techniques, it has been possible to identify some MRPs in different products derived from sugarcane, such as brown sugar and NCS, as well as in by-products, such as molasses (Supplementary Material 1).

Other phenomena may occur during the manufacturing process that could explain the fluctuating behavior of BCs throughout the entire sugarcane transformation chain. Some phytochemicals in sugarcane juices may be sensitive to pH, pressure, and temperature changes that modify their molecular structure [8]. Depending on the intensity of the treatments applied, some compounds may be destroyed, but others can be formed. For instance, it has been reported that some phenolic acids identified in molasses could come from the degradation of hydroxycinnamic acid derivatives present in sugarcane juice [8,64]. Specifically, some enzymatic processes are induced during milling that stimulate the methylation of caffeic acid to produce ferulic acid [53,64]. On the other hand, ferulic acid and vanillin can be released during the extraction of the juices due to the lignin and hemicellulose hydrolysis, both cell wall-specific polysaccharides [8].

Finally, another situation affecting the changes in the concentration of PCs during the sugarcane production process is related to the enzymatic browning processes that arise from the harvest. In this case, chlorogenic acid is well known as one of the main substrates of polyphenol oxidases, so this acid could begin to degrade once the integrity of the cells is broken [8,53]. Nevertheless, the impact of enzymatic browning reactions on PC content would not be as dramatic for products and by-products downstream of the sugarcane transformation process. Due to the high temperatures to which the juices are subjected during the clarification and evaporation process, the inactivation of the enzymes that act on the PCs would eventually be caused [64].

4. Structural description of bioactive compounds from sugarcane and its derivatives

There exists a strong relationship among several BCs found in sugarcane and its derivatives with effect on different metabolic processes evaluated *in vitro*, including antioxidant, cytoprotective, antiproliferative, antidiabetic, and antimicrobial effects. These biological activities are directly related to the chemical structure of compounds. In the case of PCs, these are a broad group of phytochemicals whose common feature is that they have at least one aromatic ring bound to one or more hydroxyl groups (-OH). The structure of PCs may have conformations varying from the simplest structure with low molecular weight to the more complex polymerized molecules [20]. Given their vast structural diversity, PCs are grouped into several categories according to the number of phenolic rings and the structural elements they join. The main classes phenolic acids, flavonoids, coumarins, tannins, quinones,

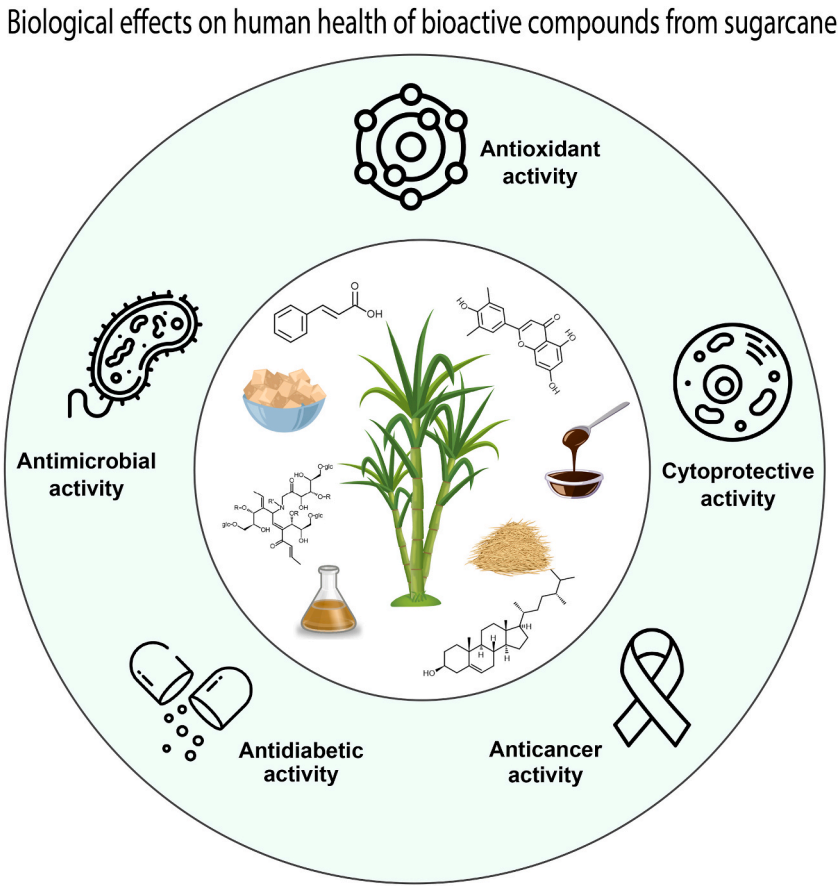

Fig. 6. Functional context in human health for BCs from sugarcane. Image by the authors.

stilbenes, and lignans [17,18,78,79]. Within each category, there are some sub-classes based on the different structural variants, for example, depending on the number and arrangement of carbon atoms, the oxidation state of heterocyclic pyran ring, or modifications in the substitution patterns of aromatic rings [80–82] (Fig. 5a and b). In sugarcane and the products generated during its processing, phenolic acids and flavonoids predominate in glycosides and aglycones form.

Terpenoids, another significant group of BCs, are a large and diverse group of compounds from the primary and secondary metabolism in plants. Therefore, they play roles ranging from the growth, development, and reproduction processes to fulfilling functions associated with the defense system and attraction of pollinating agents [83]. Chemically, terpenoids are formed by basic isoprene units organized in linear or cyclic structures that vary according to the number of constituent units and functional groups [17,18,83] (Fig. 5c). Since terpenoids possess a five-carbon molecule as a fundamental unit, its general formula can be expressed as $(C_5H_8)_n$, where n is the number of linked isoprene units. In consequence, terpenoids can be classified into hemiterpenes (C_5), monoterpenes (C_{10}), sesquiterpenes (C_{15}), diterpenes (C_{20}), sesterterpenes (C_{25}), triterpenes (C_{30}), tetraterpenes (C_{40}), and polyterpenes (from C_{45} onwards) [17] (Fig. 5c). Considering the structural and functional variety of terpenoids, several industries have focused on studying those compounds that present the highest biological activities for pharmacological and food purposes, *e.g.*, monoterpenes (such as carvacrol and thymol), sesquiterpenes (farnesol), triterpenes (phytosterols such as stigmasterol and campesterol), and tetraterpenes (carotenoids such as lycopene and lutein); either in their free forms or as conjugated glucosides (steroid glycosides such as saponins) [17,18].

Concerning, MRPs, these are a mixture of hundreds (or even thousands) of organic compounds with varying molecular weights that form during a series of complex reactions between free amino and carbonyl groups [76,77]. Due to the multiple factors that affect the Maillard reaction (*e.g.*, type and concentration of the reactant molecules, reaction time and temperature, water activity, and pH), the final composition of MRPs has not yet been fully described. However, it has been found that, within the group of MRPs, melanoidins are the main ones responsible for the biological activities demonstrated *in vitro* [77,84]. Melanoidins are a heterogeneous group of MRPs that affect the color, flavor, and texture of processed foods and influence consumer acceptance [85]. Besides, they show various health-promoting properties acting as antioxidant, antimicrobial, antihypertensive, antiallergenic, and prebiotic agents [84,86]. Due to their diversity and complexity, the chemical structure of melanoidins remains relatively unknown [77,85]; however, from the study of sugar-amino acid model systems, it has been possible to suggest some representations of its molecular conformation (Fig. 5d), as well as its empirical formula ($C_{(17\text{-}18)}\ H_{(26\text{-}27)}\ O_{10}\ N$) [87–90]. The current scientific evidence shows that melanoidins are molecules of anionic nature, with a significant presence of nitrogen, and configurations that can vary from low molecular weight structures to complex polymers [85,91,92]. These features and others that continue in research confer to melanoidins their bioactive properties as antioxidant, antimicrobial, antihypertensive, anti-inflammatory, and anti-cancer agents [77,84,85,93,94].

5. Functional description of bioactive compounds as human health-promoting agents

BCs have shown several beneficial effects for human well-being and health (Fig. 6) [4,15]. Generally, these effects are related to their molecular structure, which favors binding to specific targets, and often makes them ideal for readily penetrating cell membranes and perturbing the biological/physiological response of cells at different levels (*e.g.,* at genomic, transcriptomic, proteomic, or metabolomic level) [95]. However, in many cases, these affectations can occur synergistically due to the simultaneous action in multiple targets or signaling pathways [96]. Due to this, it is necessary to elucidate the corresponding mechanisms of action of the BCs to recognize and understand the directionality of the observed phenotypical responses. Regarding this point, our research group is currently evaluating the cellular effects of different BCs from sugarcane molasses and vinasses. In our preliminary results, a cellular response derived from exposure to the evaluated BCs has been recognized, where the affectation of specific molecular processes is indicated (data not shown). These results require further exploration to understand and describe the sensitivity of cells to BCs. Next, some biological activities of BCs from sugarcane and its derivatives as human health-promoting agents are presented.

5.1. Antioxidant and cytoprotective activity

Among all biological activities demonstrated by BCs from sugarcane, its products, and by-products, antioxidant capacity presents the highest number of reports found in the literature. Considering the structure of PCs, terpenoids, and melanoidins, the prevalence of antioxidant function is not surprising since the molecular conformation of these compounds make them key elements in preventing and combatting oxidative damage, performing a protective role in several contexts. For terpenoids and PCs, it has been suggested that their antioxidant role depends on their conjugated double bonds and the number and position of functional groups [97]. Phenolic acids, for example, owe this biological activity to the location of –OH groups with concerning carboxyl groups, so hydroxycinnamic acids are more efficient than hydroxybenzoic acids. Meanwhile, flavonoids that exhibit a higher hydroxylation degree may have an antioxidant or pro-oxidant effect, depending on their location and concentration [80]. About melanoidins, certain features have been found that give them typical behaviors of hydrophilic anionic structures, which have been positively correlated with antioxidant responses [77,90,92,93]. Based on these previous ideas, the structure-activity relationship of PCs, terpenoids, and melanoidins points to several direct and indirect antioxidant mechanisms of action, which attend to some properties of these compounds, *e.g.,* their high reducing power, their ability to binding to metal ions and form inactive complexes, their ability to trap positively charged electrophilic species, their inhibitory capacity of pro-oxidant enzymes, and even their potential to protect or enhance the cell endogenous antioxidant systems [77,80,81,84,85,90,92,97–99].

In studies about antioxidant properties of PCs, terpenoids, and melanoidins found in sugarcane and its derivatives, the viability of these molecules for free radical scavenging and chelating transition metal ions has been evaluated. For this purpose, it is usual to apply

spectrophotometric methods based on hydrogen atom transfer (HAT) or single electron transfer (SET) reactions between a sample and a radical, a radical cation, or a conjugate. These methods monitor changes in optical density as an end-point indicator of reaction [97,100–103]. Among the most applied tests are DPPH, ABTS, FRAP, ORAC, and β- CLAMS, which have been adopted and adapted to analyze extracts obtained from several sugarcane products and by-products. Due to the existence of multiple tests to measure the antioxidant power of a substance, confusion has arisen over the interpretation of the results since the reactions evaluated in *in vitro* tests do not represent the reality of living organisms. Accordingly, it is impossible to infer that the antioxidant properties demonstrated by a compound evaluated with these tests can have a meaningful physiological impact on treating diseases [16,101,102,104]. Although exploration of the antioxidant activity *in vivo* of BCs from sugarcane and its derivatives has been scarce, some studies have shown the potential of sugarcane juices as an excellent source of functional antioxidant molecules [52,105]. Specifically, there is evidence about the influence of a phenolic extract obtained from sugarcane juice in rats exposed to sub-chronic toxicity by methylmercury chloride (*MeHgCl*), a known neurotoxic agent and anorexia inducer. Because of the action of this extract, a reduction in the mortality rate of intoxicated animals and an inhibition of spontaneous lipid-peroxidation of brain cells was observed [52]. Because of this research, the protection exerted by the sugarcane juice phenolic extract against the damage produced by free radicals in the brain tissue of model organisms was evidenced. Besides, aqueous extract from sugarcane stalks have been evaluated on the nematode *Caenorhabditis elegans* and rat cortical brain slices exposed to three neurotoxic agents: toxin 6-hydroxydopamine, quinolinic acid, and ferrous sulfate. Therein, it was found that the sugarcane extracts showed a cytoprotective effect under all conditions evaluated *in vitro* and *in vivo*. This response was attributed to the PCs found in sugarcane stalks [105].

Another alternative to estimate the possible antioxidant action in living organisms is evaluating the different responses of oxidative damage caused by free radicals. In this subject, the antioxidant capacity of the compounds extracted from different sugarcane matrices to avoid mutation phenomena in organisms such as *Salmonella typhimurium* has been demonstrated [106]. Moreover, a protective effect on DNA molecules against damages caused by radiation and peroxyl and hydroxyl radicals has been demonstrated [59,65,67,107–109]. This cytoprotective potential is quite interesting since it could help to prevent DNA strands breakage and, eventually, the induction of mutagenesis, carcinogenesis, and aging processes [107–110].

Changes in different cells and cell lines subjected to oxidative stress and treated with sugarcane-origin extracts rich in BCs have also been explored. Studies in human HepG2 cells [70], NIH 3T3 fibroblasts [59], normal human dermal fibroblasts [65], rat liver Clone 9 cells [111], and erythrocytes [59] have evaluated some variables such as cell viability; intracellular levels of reactive oxygen species (ROS); losing of plasmatic membrane integrity; mitochondrial membrane potential; antioxidant activity of enzymes such as superoxide dismutase, catalase, and glutathione-peroxidase; and concentration of reduced glutathione, among others [59,70,111]. From these analyses, positive regulation of the natural defense system of the cells has been evidenced, which highlights the cytoprotective potential of sugarcane BCs against the damage caused by free radicals in biological systems [59,111].

Considering all these antioxidant properties demonstrated *in vitro,* and the limitations concerning scaling to *in vivo* conditions, the practical applications of PCs, terpenoids, and sugarcane melanoidins at a clinical level require in-depth research where all factors associated with metabolism are analyzed [16]. However, the results of tests like DPPH, ABTS, FRAP, or ORAC can be considered as a quality indicator for the valorization of sugarcane products and by-products. So, one of the most feasible practical applications would be at the industrial level when to obtain natural antioxidant compounds that improve the stability of foodstuffs (*e.g.,* preventing protein oxidation and lipid rancidity) and make them safer for consumers [67,77,80].

5.2. Antineoplastic activity

One of the most severe consequences of the action of free radicals on biomolecules is the development and progression of cancer [79]. For example, some ROS, as second messengers in several pathways, could increase cell proliferation, resistance to apoptosis, and proto-oncogenes activation [112]. In line with this, a valid assumption that could arise is that BCs with antioxidant properties derived from interaction with ROS would have the ability to inhibit the processes of cellular transformation and cell proliferation. In this respect, a positive correlation between some phytochemicals with antioxidant properties and some antineoplastic effects has been observed [21,99,112].

It is interesting to observe how some antioxidant compounds found in sugarcane and its derivatives have also revealed antiproliferative effects. For example, in a phenolic extract from sugarcane juices, a glycoside derived from tricine (tricin-7-*O*-β-(6″-methoxycinnamic)-glucoside) was identified as capable of acting as a free radical scavenger and inhibiting the proliferation of cancer cell lines such as MCF-7, NCI-ADR/RES, NCI 460, UACC62, 786-0, OVCAR03, PC03, and HT-29 [49]. Similarly, some terpenoids and PCs from sugarcane leaves and stalks extracts, mainly tricine, shown inhibitory effects for cell growth in OVCAR-03, NCI-ADR/RES, and HaCat cancer cell lines [113]. On the other hand, antiproliferative activity has been confirmed for crude extracts of sugarcane rinds on HT29 cell lines, attributing this response to PCs present in the extract, mainly to anthocyanins [34]. Finally, a couple of studies verified the cytoprotective and antiproliferative properties of phenolic acids from sugarcane leaves on human HepG2 cells and Clone 9 cells exposed to oxidative stress [111,114].

Molecular mechanisms exhibited by PCs and terpenoids to interfere with carcinogenesis go beyond their protective role against oxidative damage [21]. Due to the molecular structure of these compounds, they could promote non-covalent interactions with other molecules that trigger cell events leading to cancer initiation, promotion, and progression. Some of these events are regulation of tumor-suppressor-genes and oncogenes expression, inhibition of oncogenesis-promoting enzymes, apoptosis induction and cell cycle arrest, modulation of some signal transduction pathways, and stimulation of carcinogens elimination processes [21,112,115,116]. Events like these can explain some findings about the antiproliferative capacity attributed to PCs and their correlation with the reduction of the mitochondrial membrane potential and the increase of the activity in caspase 3, one of the main enzymes responsible

Table 1
Microorganisms inhibited by BCs found in extracts from sugarcane and its derivatives.

Microorganisms	Compounds related to inhibitory activity	Sources from sugarcane	References
Escherichia coli	Chlorogenic acid, ferulic acid, gallic acid, p-coumaric acid, p-hydroxybenzoic acid, phenylvaleric acid, quinic acid, sinapic acid, syringic acid, tannic acid, apigenin.	Leaves, rind, stalks, roots, bagasse, molasses.	Hussain et al. [153]; Juttuporn et al. [40]; Khaliq et al. [130]; Shafiga-Atikah et al. [154]; Uchenna et al. [127]; Williams et al. [155]; Zhao et al. [42]
Staphylococcus aureus	Chlorogenic acid, ferulic acid, gallic acid, p-coumaric acid, phenylvaleric acid, quinic acid, sinapic acid, syringic acid, tannic acid, apigenin.	Leaves, rind, stalks, bagasse, molasses.	Hussain et al. [153]; Juttuporn et al. [40]; Shafiga-Atikah et al. [154]; Uchenna et al. [127]; Williams et al. [155]; Zhao et al. [42]
Listeria monocytogenes	Chlorogenic acid, ferulic acid, gallic acid, p-coumaric acid, p-hydroxybenzoic acid, phenylvaleric acid, quinic acid, sinapic acid, tannic acid, apigenin.	Bagasse, molasses.	Shafiga-Atikah et al. [154]; Zhao et al. [42]
Salmonella typhimurium	Chlorogenic acid, ferulic acid, gallic acid, p-coumaric acid, p-hydroxybenzoic acid, sinapic acid.	Leaves, bagasse.	Hussain et al. [153]; Zhao et al [42]
Salmonella enterica	Gallic acid, phenylvaleric acid, quinic acid, tannic acid, apigenin.	Molasses.	Shafiga-Atikah et al. [154]
Streptococcus mutans	Caffeic acid, chlorogenic acid, ferulic acid, p-coumaric acid, apigenin, tricin, luteolin.	Molasses, NCS.	Barrera et al. [58]; Takara et al. [69]
Streptococcus sobrinus	Caffeic acid, chlorogenic acid, ferulic acid, p-coumaric acid, apigenin, tricin, luteolin.	Molasses, NCS.	Barrera et al. [58]; Takara et al. [69]
Streptococcus aureus	Not specified.	Bagasse.	Velázquez-Martínez et al. [156]
Bacillus cereus	Not specified.	Bagasse.	Velázquez-Martínez et al. [156]
Bacillus subtilus	Not specified.	Leaves, roots.	Hussain et al. [153]; Khaliq et al. [130]
Bacillus lichenformis	Not specified.	Vinasse.	Kaushik et al. [74]
Pseudomonas aeruginosa	Not specified.	Leaves, rind, stalks.	Hussain et al. [153]; Uchenna et al. [127]; Williams et al. [155]
Pseudomonas putida	Not specified.	Vinasse.	Kaushik et al. [74]
Klebsiella pneumoniae	Not specified.	Stalks.	Hussain et al. [153]; Williams et al. [155]
Candida albicans	Not specified.	Stalks.	Hussain et al. [153]; Williams et al. [155]
Aspergillus sp.	Not specified.	Juice.	Racowski et al. [131]
Aspergillus fumigatus	Not specified.	Stalks.	Williams et al. [155]
Rhizopus solani	Not specified.	Roots.	Khaliq et al. [130]
Fusarium sp.	Not specified.	Juice.	Racowski et al. [131]

NCS: Non-centrifugal sugar.

for the apoptotic process [111].

Finally, regarding MRPs, the antineoplastic capacity of melanoidins has previously been reported [84]; however, these have not been investigated for products and by-products from sugarcane, so this constitutes an exciting opportunity for this industry.

5.3. Antidiabetic activity

Diabetes mellitus is a group of metabolic disorders characterized by a dysfunctional activity of insulin, either by the ineffective action of this hormone, by the inability of the pancreas to secrete it, or by the occurrence of both events. According to its etiology, there are four types of diabetes: type 1 diabetes (T1DM), type 2 diabetes (T2DM), gestational diabetes, and other types of diabetes. T2DM is the most common worldwide, representing between 90 and 95% of diagnosed cases. This prevalence is strongly related to growing bad dietary habits and unhealthy lifestyles [12,117]. Consequently, T2DM management includes the reduction or elimination of risk factors by improving diet and physical activity. Additionally, there are some clinical treatments such as exogenous insulin therapy or oral medications such as sulphonylureas, biguanides, meglitinides, thiazolidinediones, analog peptides, aldose reductase inhibitors, and α-glucosidase inhibitors [117–119]. Considering that currently available pharmacological agents are not entirely effective and have specific undesirable side effects, in recent years, different studies have opened the way to identify natural BCs with antidiabetic potential that can avoid the adverse effects of conventional treatments [117,118]. Among the most studied phytochemicals are PCs, which work by several mechanisms, either reactivating the pancreatic functions of β-cells, increasing the sensitivity of the target tissues to insulin, modulating the activity of enzymes involved in glucose metabolism, reducing the intestinal absorption of carbohydrates, or acting on ROS [47,78,98]. Some studies have presented possible explanations for the antidiabetic mechanisms of PCs at the molecular level [78,98]. Among the PCs explored are apigenin, quercetin, catechin, and genistein, which have been identified in sugarcane and some of its derivatives (Supplementary Material 1).

Antidiabetic effects reported by BCs from sugarcane and its derivatives have shown to exert an inhibitory influence on α-glucosidase and α-amylase. This response delays the digestion of complex carbohydrates and the absorption of glucose in the small intestine, resulting in a slow passage of glucose into the blood plasma and, consequently, a general reduction in postprandial glucose levels [51,68,119]. This has been reflected in several studies conducted *in vitro* and *in vivo* conditions, in which products such as sugarcane juice, different types of sugar, NCS, bagasse, and molasses have been evaluated [43,51,68,71,120–122]. Specifically, it has been noticed that different extracts from sugarcane bagasse exhibit inhibitory activity on α-glucosidase with effects that improve with increasing extracts concentration [43]. In this regard, it has been indicated that 10 mg/mL of bagasse extract with a 30% hydro-alcoholic fraction is enough to reduce enzymatic action by up to 82.64% [43]. Regarding molasses, the response of α-glucosidase and α-amylase to molasses extracts at different concentrations was previously explored [68]. Therein, it was found that the enzymatic activity decreased when the extract was more concentrated. This behavior was explicitly associated with the caffeic and ferulic acids found in the extracts. These results established that the average concentration required to inhibit enzyme activity by 50% (IC_{50}) was 4.693 mg/mL for α-glucosidase and 4.254 mg/mL for α-amylase [68].

Additional studies showed a similar positive effect on pancreatic functions reactivation of β-cells [71], where sugarcane molasses at low concentrations (0.5 mg/mL) has a regulatory effect on the activity of dysfunctional pancreatic β-cells in rats. Based on these findings, molasses could be used as raw material to extract BCs with potential pharmacological uses and would also be helpful as a functional food for the T2DM treatment [68,123]. Interestingly, the potential of molasses as a nutraceutical product has been evidenced in some studies, where it was shown that oral administration of an aqueous concentrate of filtered molasses given to a group of test subjects just before their traditional breakfast could decrease the plasmatic glucose concentrations after meals [120,122]. This evidence would make sugarcane molasses a promising source of low glycemic index foodstuffs, whose continuous intake would mitigate the effects of metabolic stress on β-cells and the progression of insulin resistance [120,122].

5.4. Antimicrobial activity

Several studies show the effectiveness of sugarcane BCs in combating different microorganisms or inhibiting their growth (Table 1). Extracts obtained from sugarcane leaves, roots, rinds, and various products and by-products such as bagasse, juices, molasses, and vinasses have shown antibacterial or antifungal actions that have been related to some BCs coming both from plant secondary metabolism and from the manufacturing processes. However, most of the published information so far highlights PCs as the main compounds responsible for the antimicrobial properties of sugarcane products.

Understanding that plants synthesize some BCs as a natural defense system against microbial attacks, it is expected that these compounds may exhibit certain influence *in vitro* on some microorganisms [124,125]. Indeed, it has been found that the antimicrobial capacity of PCs is associated with their molecular structure, in which the presence of aromatic rings predominates. Thus, there is a positive correlation between the amount and position of hydroxyl groups and microbial inhibition, revealing increasing toxicity the higher –OH groups number in molecules [124,126]. Specifically, the antimicrobial activity of flavonoids could be attributed to their lipophilic character [91,124]. Thereby, depending on the molecular structure of PCs, they can act by mechanisms associated with the cell surface, or interfere with metabolic processes at intracellular level. As a result of interactions between PCs and cell membranes, death or growth inhibition of microorganisms can occur, either due to losing membranes functionality and integrity or due to the penetration of these compounds into intracellular space, promoting antimicrobial function derived from interactions with specific targets [17,69,91,127].

In the first case about cell surface antimicrobial mechanisms, the effects of PCs could be based on molecular interactions between these compounds and plasmatic membranes, which are promoted by factors such as pH, aromatic ring substitutions, and saturation of

sidechain of molecules [128]. Due to these interactions, alterations occur in hydrophilic and hydrophobic regions of the cell membrane, leading to increased permeability, pore formation, or, eventually, cell death [17,129]. Flavonoids, for example, have a particular ability to interact with cell membranes and walls, allowing them to form complexes with proteins that inhibit microbial growth by suppressing virulence factors such as quorum-sensing signal receptors [17,82,124,128]. Regarding the intracellular antimicrobial mechanisms of PCs, compounds whose activity is based on crossing the membranes and finding their targets inside the cells have been found. Thereby, BCs get involved in different metabolic processes that inhibit the growth of microorganisms or lead to their death. Among the cellular processes affected by BCs are those related to energy metabolism [17,18,129], deprivation of substrates necessary for microbial growth [17,18,128], impeding the synthesis of proteins and nucleic acids [17,18,127], stopping the activity of certain enzymes (*e.g.,* DNA-gyrase [18] and glycosyltransferase [69]), and interrupting DNA replication, repairing, and recombination processes [18].

Although PCs affect a broad spectrum of microorganisms, the structural diversity of these compounds could influence their mode of action on a particular target. For instance, lower molecular weight phenolic acids diffuse more efficiently through plasmatic membrane, bringing consequences such as intermembrane pores formation and cytoplasm acidification [42,128]. Meanwhile, more complex molecules, like flavonoids, interfere with crucial intracellular processes for cell viability [18,127]. Thus, any of these effects occur differently in prokaryotic and eukaryotic organisms due to the difference in composition and fluidity of cytoplasmic membranes and cell walls. These aspects, added to factors such as the molecular diversity of PCs, their concentration, and incubation time, could regulate the passage of compounds into the cells. The bacterial response to sugarcane BCs illustrates this behavior since differences between Gram-negative and Gram-positive organisms have been noted, showing better inhibitory results on the latter. For example, in the study of the antimicrobial potential of sugarcane root extracts, a lower minimum inhibitory concentration (MIC) was observed for *Bacillus subtilus* (G+) compared to *Escherichia coli* (G−) (with values between 0.198 and 0.327 mg/mL for *B. subtilus* and between 0.226 and 0.387 mg/mL for *E. coli*) [130]. Similarly, it has been reported a MIC for sugarcane bagasse extract of 0.625 mg/mL for *Staphylococcus aureus* and 1.25 mg/mL for *Listeria monocytogenes*, both Gram-positive bacteria [42]. Besides, for Gram-negative bacteria, *E. coli* and *Salmonella typhimurium* were higher, with MIC of 2.5 mg/mL in each case [42]. These differences can be understood due to the surface morphology of both types of bacteria. Because the outer membrane of lipopolysaccharides surrounds the cell wall of Gram-negative bacteria, a kind of barrier is created that restricts the diffusion of hydrophobic compounds through the cytoplasmic membrane, making these microorganisms more resistant than Gram-positive bacteria lacking this envelope [42,130]. About that, morphological changes have been observed in different microorganisms exposed to extracts of sugarcane bagasse, revealing peripheral and internal damage that severely compromises their survival, and that would demonstrate the superficial and intracellular mechanisms of action of PCs [42].

Regarding fungi, previous studies have shown that the MIC of sugarcane roots extract on *Rhizopus solani* was between 0.221 and 0.271 mg/mL [130], while strains of *Aspergillus* sp. and *Fusarium* sp. showed growth inhibition of colonies up to 83.5 and 41.1%, respectively, after 48 h of incubation with sugarcane juice extracts [131]. Although there is no report about a specific mechanism by which these microorganisms are sensitive to the BCs present in analyzed samples, it could be thought that the antifungal effect would be related to the unique cellular structure of fungi. Fungi have a highly dynamic porous cell wall composed of chitin microfibrils, glycan chains, and glycoproteins connected to the plasmatic membrane through an anchoring glycolipid: glycosylphosphatidylinositol [132]. Besides, the lipid bilayer of the fungal cell membrane is constituted by ergosterol instead of cholesterol [133]. Although these two unique characteristics of fungi could explain the effectiveness of sugarcane antifungal compounds, this hypothesis must be deeply explored.

At last, regarding the antimicrobial properties of compounds formed during sugarcane processing, it has been found that this function is partially exerted by MRPs, mainly melanoidins [85,91,94]. Previously, it has been reported that melanoidins exert an inhibitory effect on some microbial enzymes involved in protein breakdown processes [91]. Additionally, these compounds have shown genotoxic effects due to the formation of complexes with some metals (*e.g.,* Cu^{2+}), where the reduced metal radical triggers the breakdown of DNA molecules [91]. These specific effects of melanoidins found in the refineries by-products, adjust to the mechanisms by which these MRPs lethally affect microorganisms. Due to their anionic charge and their ability to act as chelating agents, melanoidins can disturb the outer membranes when chelating the Mg^{2+} ions, promoting disruption of bacterial inner membranes, and releasing intracellular content [77,84,93]. All these responses of the microorganisms to MRPs, as well as those manifested by the PCs influence, could be highly appreciated, either for therapeutic purposes or in industrial applications, for example, for food preservation.

6. Omics approaches to the study of bioactive compounds from sugarcane

As an outcome of the scientific and technological advances achieved in the post-genomic era, the way has been opened to holistically analyze the molecules produced by a cell, tissue, or organism at a given moment, as well as the biological activities that these molecules can exhibit. Consequently, a change of focus has been achieved in the study of BCs, going from identifying and isolating a few individual compounds to more massive and multiscale analyses. With this change, it has been possible to describe the metabolic profile of biological samples and to monitor changes occurring in these profiles in response to different conditions or treatments applied. Besides, it has contributed to the more accurate evaluation of the effects of BCs in *in-vitro* conditions and in living models [11,134–136]. All these advances have reinforced some of the study fields of omics sciences, mainly metabolomics and foodomics, since due to the emergence of nutraceutical foods and ingredients, a direct connection has been established between the BCs intake and their health influence. This undoubtedly affects the food production systems and the conservation processes to ensure foodstuff quality and safety [11,134,137].

6.1. Metabolomic approach

Metabolomics is the systematic study of small molecules obtained as primary and secondary metabolic products of a biological system (metabolome), from cellular to organismic scale at a given time. It has been estimated that plants produce approximately 100.000–200.000 metabolites, depending on genomic complexity [134,138]. Several authors have pointed out that sugarcane metabolomics is in an incipient stage of development due to difficulty in determining stable functional molecules and markers for complex traits [138–140]. However, valuable efforts have been made to build the sugarcane metabolome. For instance, in 2003 [141] and 2007 [142], between 30 and 55 metabolites associated with plant stalks development and sucrose accumulation in internodes were identified. These findings represented a significant advance since they could be considered as one of the first approaches to the metabolite profile of sugarcane.

Compared to predecessor disciplines of metabolomics (genomics, transcriptomics, and proteomics), studying metabolomes is a higher step in the complexity scale. Since metabolites are the final receptors of the flow of genetic information, multiple factors exist involved in their biosynthesis. Therefore, any variation, either at the gene level or protein level, will be reflected in the metabolic profiles [135]. Accordingly, based on a metabolomic approach, an important aspect to consider for studying sugarcane BCs is the expression of genes associated with the biosynthesis of secondary metabolites. Despite the challenge posed by such studies in a complex polyploid plant such as sugarcane, in times close to the birth of the omics revolution, the gene expression profile associated with the synthesis of enzymes involved in the terpenoid and PCs pathways was characterized, so it was possible to obtain a preliminary metabolic profile of sugarcane and to know its changes derived from the action of biotic agents and abiotic [23]. On the other hand, and as a result of a more massive analysis, a significant profile of 56 metabolites, including phenolic acids, flavones, and their glucoside derivatives, was defined for 13 different sugarcane genotypes [27]. Similarly, in more recent studies, metabolomics allowed a large-scale determination of the metabolite profile of sugarcane products and by-products [51,143,144]. Particularly for juices and molasses, it was possible to identify 42 metabolites (including flavonoids, fatty acids, and terpenoids) with confirmed effects as antioxidants and antihyperglycemic agents *in vitro* [51].

A critical factor in metabolomics is the large amount of information generated by each assay, which makes it necessary to implement robust bioinformatics and statistics tools that facilitate data processing and analysis [135,145]. The application of comparison and alignment methods and tests such as principal component analysis (PCA), simultaneous component analysis (SCA), hierarchical cluster analysis (HCA), partial least squares (PLS), back-prop artificial neural networks (BANN), and discriminant analysis (DA), among others, has promoted the creation of specialized databases, tools, and resources (Table 2) that remain in continuous improvement and represent a valuable source of information to increase the understanding of processes related to biosynthesis and function of secondary metabolites in biological systems [135,139,140,145,146].

Thanks to the development of analytical and computational tools for metabolomic studies, it is possible to advance in the research of BCs following *in silico* procedures, which allow associating genes to metabolites and metabolites to genes under a perspective called retro-biosynthetic approach [147]. This paradigm shift could lead to the full knowledge of cellular machinery required for the activation of biosynthetic pathways of industrially interesting secondary metabolites, which would become a significative advance for the mass production of phytochemicals with potential biological activities, and for the prediction of promising BCs [147].

6.2. From metabolomics to trans-omics approach

One field that have been favored by omics expansion is related to food science in a branch known as foodomics. This discipline transversally integrates the tools provided by genomics, transcriptomics, proteomics, and metabolomics to study foodstuffs and their effects on the health and well-being of those who consume them [136,137]. Within the foodomics field, nutrigenomics is a sub-area of

Table 2
Common databases, tools, or bioinformatical resources applied in the study of the biosynthesis and function of BCs in biological systems.

Database	URL	References
Kyoto Encyclopedia of Genes and Genomes (KEGG)	http://www.genome.jp/kegg/	Kanehisa and Goto [157]
The Human Metabolome Database (HMDB)	https://hmdb.ca/	Wishart et al. [158]; Wishart et al. [159]
BioCyc	https://biocyc.org/	Karp et al. [160]
MetaboAnalyst	https://www.metaboanalyst.ca/home.xhtml	Xia et al. [161]
MetaboLights	https://www.ebi.ac.uk/metabolights/index	Haug et al. [162]
Golm Metabolome Database (GMD)	http://gmd.mpimp-golm.mpg.de/	Hummel et al. [163]; Kopka et al. [164]
KNApSAcK Metabolomics	http://www.knapsackfamily.com/KNApSAcK/	Nakamura et al. [165]
METLIN	https://metlin.scripps.edu	Guijas et al. [166]
Competitive Fragmentation Modeling for Metabolite Identification (CFM-ID)	http://cfmid.wishartlab.com/	Allen et al. [167]; Wang et al. [168]
Plant Metabolic Network (PMN)	https://www.plantcyc.org/	Hawkins et al. [169]
ReSpect for Phytochemicals	http://spectra.psc.riken.jp/	Sawada et al. [170]
Secondary Metabolite Bioinformatics Portal (SMBP)	http://www.secondarymetabolites.org/	Weber and Kim [171]
Electronic BioActive Substances Information System (eBASIS)	https://ebasis.eurofir.org/	Plumb et al. [172]

particular importance that describes how foods affect gene expression profiles [137,148,149]. In the BCs context, although research has been oriented toward understanding their synthesis, biological properties, molecular targets, and mechanisms of action, studying these compounds could also be carried out under nutrigenomics orientation. Besides, since plant products are a fundamental part of the diet, any change in their metabolism or industrial transformation processes could affect the composition of foods and their potential nutraceutical activities [137]. Hence, the implementation of nutrigenomic studies would allow understanding the molecular and biochemical mechanisms related to the cellular response to the bioactive components of the diet and their influence on human health [150].

Considering that several BCs can affect numerous molecular targets and exhibit multiple physiological effects (even simultaneously), these compounds and their implications could be analyzed by implementing different technologies across multiple omics scales, incorporating a *trans*-omics study approach [151]. For instance, whole genome or transcriptome sequencing processes could be applied by next-generation technologies (NGS) together with chromatographic separation and massive characterization of proteins, lipids, or metabolites through different techniques coupled to mass spectrometry (MS) or nuclear magnetic resonance (NMR). With this, helpful information would be provided to perform wide association studies to specific traits, which would allow the designing preventive and therapeutic strategies that reduce the risks associated with different diseases [11,151].

From reviewing scientific information available to date, no research has been found that reports the adoption of the *trans*-omics approach to know the molecular processes activated or inhibited in biological systems by the exposure to sugarcane BCs. This is an excellent opportunity to continue deepening the understanding of the mechanisms of action of BCs as human health promoters, since from the knowledge generated from the application of multi-omics tools at nutrition and food science service, it hopes that cause-effect correlations can be established to contributing to the formulation of more and better prevention and intervention procedures for different chronic diseases [11,136].

7. Final considerations

Although sugarcane agroindustry has maintained a constant motivation for searching for more and better production conditions, this has not been exclusive for supplying commodities like sugar. Indeed, the diversification and development of new products with higher added value have led to a great researching deployment that transcends the biomass generation for biofuel production and energy cogeneration. The identification of biologically active compounds has opened a huge opportunity to venture into industrial applications like nutraceuticals products. Thanks to the proven antioxidant, cytoprotective, antiproliferative, antihyperglycemic, and antimicrobial properties of sugarcane by-products, it is possible to think in a better use for materials such as bagasse, filter mud, molasses, and vinasses. However, for compounds such as PCs, terpenoids, and MRPs obtained from those sources to be incorporated into foodstuffs as strategies for preventing or treating diseases, it is necessary to deepen into some relevant issues. Among the most critical aspects to be examined are the molecular stability of bio-compounds in food matrices and their preservation during storage, the bioavailability of molecules inside the body after food intake, the molecular mechanisms involved in the biological function of compounds, and possible side effects. The study of these critical aspects implies methodological challenges, for example, *in vivo* experimental designs and modeling of predictive processes *in silico*, which can be successfully addressed thanks to massive applicating tools of genomics, transcriptomics, proteomics, and metabolomics, all of them transversely combined through a more comprehensive perspective: foodomics.

Credit author statement

Andrea Molina-Cortés: Conceptualization, methodology, and writing. Mauricio Quimbaya: Conceptualization and methodology. Angie Toro-Gomez: Data curation and visualization. Fabian Tobar-Tosse: Supervision, conceptualization, writing-reviewing, and editing.

Ethical approval

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Declaration of competing interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

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