INTERNATIONAL JOURNAL OF AGRICULTURE & BIOLOGY
ISSN Print: 1560–8530; ISSN Online: 1814–9596
22–0084/2022/27–5–341–360
DOI: 10.17957/IJAB/15.1935
http://www.fspublishers.org

Review Article

Biological Activity of Avocado By-Products: A Review Focusing on Farm Animals' Health

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Received 18 February 2022; Accepted 30 April 2022; Published 26 May 2022

Abstract

The avocado industries produce a large amount of waste, which constitutes a threat to the environment. In this work, the complete set of bioactive compounds from avocado by-products (AP), their biological activities, and the experimentation accomplished using AP in farm animals' diets are reviewed. AP, that is seeds and peels, are raw sources of phenolic compounds (flavanol monomers, procyanidins, and hydroxycinnamic acids), furan derivatives, aliphatic acetogenins (which have antimicrobial and spore germination inhibiting effects), carotenoids, phytates, polyols, and sterols. Moreover, AP contain valuable nutrients (proteins, lipids, and carbohydrates) that could effectively contribute to farm animals' diets. Among the biological properties of AP, highlight their antimicrobial, antioxidant, and anti-inflammatory ones. Ill effects of avocado by-products seem to be animal species-dependent, given that AP has been cited as conditionally toxic for some animals. Conversely, feeding AP has positive effects on pigs, and these have been used successfully to feed goats and sheep, and in aquaculture. To use AP as livestock feed, the excessive amount of bioactive compounds could be decreased by hydrothermal treatment. This was successfully applied to avocado seeds to reduce bioactive compounds and fiber contents to safe levels. Overall, AP could be used for extracting healthy compounds to be used as nutritional supplements, and for improving the health of selected farm animals. Furthermore, AP-derived compounds could be useful in reducing the emergence of antibiotic-resistant bacteria, which has been linked to the abusive use of antibiotics when used as growth promoters in farm animals' production.

Keywords: Avocado by-products; Phenolics; Furans; Acetogenins; Antioxidant; Farm animals

Introduction

Avocado (*Persea Americana* Mill.) is the most important crop within the Laurel family (Lauraceae). This tropical tree produces an oily fruit used by indigenous people for at least 9,000 years and obtained in the wild in Meso-America, which was appreciated by Mayan and Aztec civilizations (Storey *et al.* 1986). Today, this fruit is quickly distributed in all regions of the world due to its favorable nutrient properties: it contains a large amount of monounsaturated fatty acids (FA) and valuable quantities of vitamins, minerals, and phytochemicals (Schaffer and Wolstenholme 2013). The fruits of avocado are mainly used for human consumption and to produce cosmetics, nutritional supplements, and livestock feed. The avocado pulp is generally used for culinary purposes, while the seeds and peels are usually disposed of by landfilling. In 2019, the world avocado production was 7,308,978 Tm (FAO, 2019), and from this production, the avocado by-products (AP) accounted for ~54.8% (wet basis) (Negesse *et al.* 2009). Historically, avocado seeds have been used in traditional Mesoamerican medicine for the treatment of rheumatism, asthma, various infectious diseases, and also for diarrhea and dysentery induced by intestinal parasites (Jiménez-Arellanes *et al.* 2013).

The criteria for designing feed formulas are based on improving body weight (BW), feed conversion efficiency, protein accretion, and milk and egg production. Regrettably, all criteria focus on productivity rather than on achieving healthy animals, and for this antibiotics are used (Guil-Guerrero *et al.* 2016a). This use is intended to avoid gastrointestinal infections and inflammatory bowel diseases. However, antibiotics are often misused in animal production farms, and thus antibiotic residues appear in the environment (Guil-Guerrero *et al.* 2016b). For avoiding this excessive use, plant-food by-products can be introduced into the diet of farm-animal, as these contain suitable concentrations of plant-derived compounds with antimicrobial and health-enhancing properties (Guil-Guerrero *et al.* 2016c).

A major problem with AP used as food or feed supplements is that although they contain protein and carbohydrates, the high concentration of polyphenols contained in it confers a bitter taste and can reach toxicity at high levels (Domínguez *et al.* 2014). However, their use in mixes with other plant food by-products or feed will reduce such flavor to acceptable limits, while providing interesting amounts of bioactive compounds for health promotion.

Previously, AP were partially reviewed about phenolic compounds content, and some biological activities, such as antioxidant ones (Araújo *et al.* 2018). However, despite the wide research carried out on the biochemical composition and biological activities of AP, as well as the studies on its use as animal feed, still, all this research remains un-reviewed as a whole. The present review discusses all relevant data about AP, focusing on their biochemical composition and related health benefits for farm animals, while potential directions for future studies are provided.

Biochemical composition and health benefits of avocado by-products

Approximately, 100 g of fresh fruits generate 12–16 g of peel and 14–24 g of seeds (Bressani *et al.* 2009); thus, finding new uses for this by-product is a desirable action. Considering the seeds, it highlights their protein content, which is highly dependent on processing methodology, ranging from 6.24 to 23.54 g·100 g^{-1} (Talabi *et al.* 2016). The seeds also contain healthy fatty acids (FA), and the FA profiles of three avocado varieties (Fuerte, Bacon, and Hass) were studied in Japan by Takenaga *et al.* (2008). The main FA in seeds were linoleic acid (LA, 18:2*n*-6) (35.3–38.2% of total FA), oleic acid (OA, 18:1*n*-9) (22.4–22.1% of total FA), and palmitic acid (PA, 16:0) (17.7–17.9% of total FA). These FA percentages are similar to those reported by Alkhalf *et al.* (2019).

Phytochemical studies on AP identified various classes of natural products: phenolic compounds, phytosterols, polyols, furan derivatives, acetogenins, carotenoids, abscisic acid, lignans, glucosides, as well as FA and hydroxylated ones. The levels of such compounds vary according to avocado variety, farming variables, and ripeness. Measured levels are also influenced by the method of extraction during experimentation.

Phenolics occur both in peels and seeds of avocado fruits and comprise phenolic acids (Fig. 1), phenolic alcohol derivatives (Fig. 2), flavonoids (Fig. 3), and procyanidins (oligomeric tannins, Fig. 4). Total phenolic amounts deeply differ between avocado peels and seeds (Table 1). Considering total phenolics reported as gallic acid equivalent (GAE), in avocado peels these ranged from 1.40–18.94 g·kg^{-1} FW (Ramos-Aguilar *et al.* 2021) to 527.8 g GAE·kg^{-1} DW (Rosero *et al.* 2019), while total phenolics in seeds ranged from 0.30 g GAE·kg^{-1} g DW in cv. Criollo spp. (Cid-Pérez *et al.* 2021) to 292 g GAE·kg^{-1} DW in avocado seeds (Pahua-Ramos *et al.* 2012). In AP, flavonoids showed low figures, but tannins occur in amounts similar to those of phenolic acids (Lee *et al.* 2008), and anthocyanins showed variable amounts in peels (Ashton *et al.* 2006).

Phenolic profiles are summarized in Table 2. The peels extracts contain a great variety of phenolic acids, such as hydroxycinnamic and hydroxybenzoic ones, and some flavonoids such as quercetin and catechin. The seed extracts contain mainly hydroxycinnamic acids, and flavonoids such as epicatechin catechin, and procyanidins. Summarized phenolic acids show interesting properties for human health and achieving a more sustainable and cleaner animal production. Simple phenolic acids have antibacterial actions, for instance against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Listeria monocytogenes*. Saavedra *et al.* (2010) described synergy between streptomycin and phenolic acids against Gram-bacteria. Wen *et al.* (2003) indicated that phenolic acids mixtures have additive antilisterial effects, and reported a significant relationship between pH and antilisterial activity. Cueva *et al.* (2010) stated that phenolic acids act as growth inhibitors of several lactobacilli species and some pathogens (*S. aureus* and *Candida albicans*), but *P. aeruginosa* was not affected by these compounds. Flavonoids are secondary polyphenolic metabolites that have a ketone group and yellowish pigments, and the ones contained in AP have antibacterial activity. Such compounds have been successfully tested against oxacillin-resistant *S. aureus*, cariogenic *Streptococcus mutans*, and uropathogenic *E. coli*. The mechanisms related to the bacterial growth inhibition were diverse, *e.g.*, destabilization of the cytoplasmic membranes and the deprivation of the substrates required for microbial growth, such as Fe and Zn (*via* chelation of molecules with these metals), and such depletion can severely limit bacterial growth (Dixon *et al.* 2005; Heinonen 2007). Other interesting phenolics are procyanidins, which are catechin- and epicatechin-oligomeric compounds, which exhibit chemoprotective properties against cancer (Jeong and Kong 2004), improve lipid metabolism (Puiggros *et al.* 2005), prevent infections in the urinary tract, and can modulate antioxidant enzymatic activities (Puiggros *et al.* 2005), among other bioactivities.

Tannins, *i.e.*, water-soluble polyphenols, occur in avocado peel (Table 1, Negesse *et al.* 2009). These compounds, which have high molecular weight and many phenolic groups, are able to precipitate protein (Hagerman *et al.* 1998). Tannins affect rumen bacteria by inactivating several enzymes, *e.g.*, glutamate dehydrogenase, proteases, and carboxymethyl cellulase. Furthermore, sulfur and iron bioavailability is limited to animals that consume tannin-rich tissues, thus, large consumption of tannins can induce toxicity (Kumar and Vaithiyanathan 1990). The phenolic compounds contained in AP are of great interest considering that these have high diversity, and therefore a synergistic antibacterial action due to such compounds can be expected through the consumption of AP, which could help to prevent many digestive pathologies in farm animals.

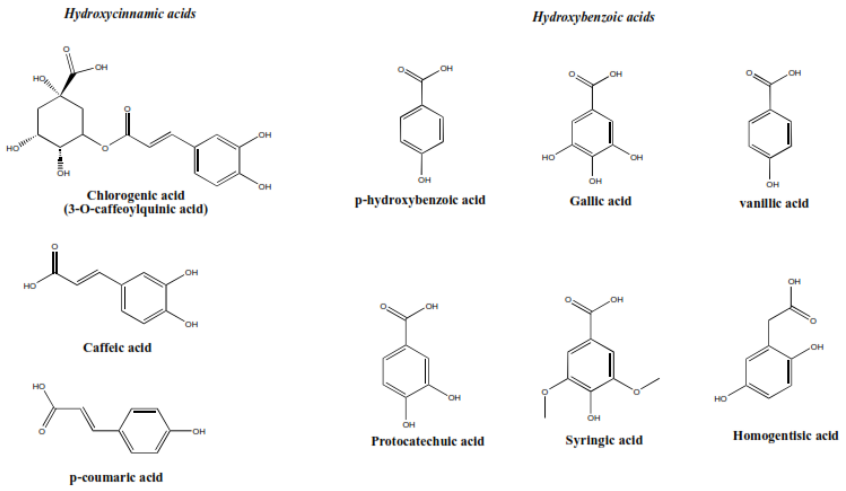

Fig. 1: Phenolic acids contained in avocado by-products

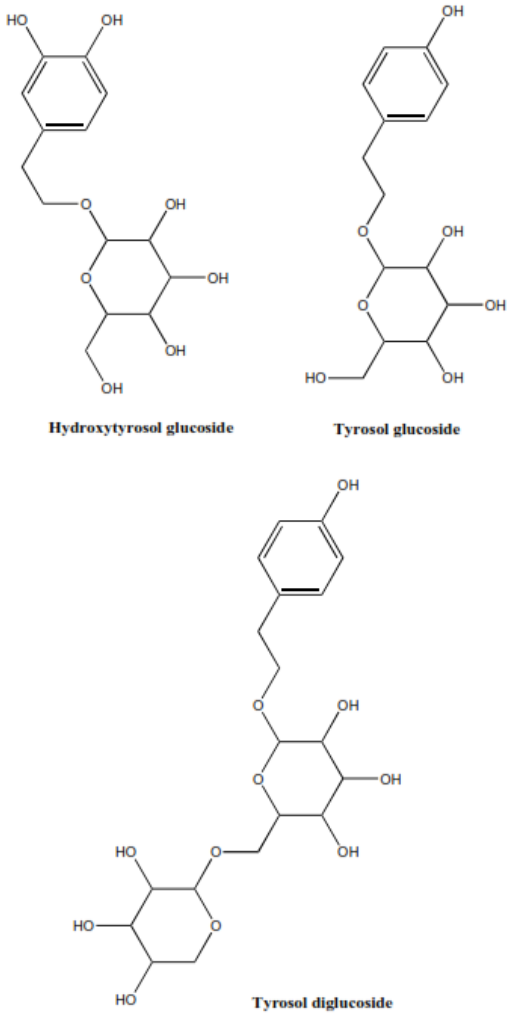

Fig. 2: Phenolic alcohol derivatives contained in avocado by-products

The occurrence of other compounds in AP is summarized in Table 3. *Furan derivatives* (Fig. 5) were found in seeds by Ding *et al.* (2007). These compounds have been subjected to structural modifications, and antibacterial, antifungal, and insecticidal activities were checked with positive results (Rodríguez-Saona and Trumble 2000). *Aliphatic acetogenins*, also known as "hydroxylated fatty alcohols", were reported by Kashman *et al.* 1969a, b, which constitute a class of compounds almost exclusively isolated from avocado (Fig. 6). These have antimicrobial, antibacterial and spore germination inhibiting effects (Hernández-Brenes *et al.* 2013), and anti-inflammatory properties were cited for the acetogenins isolated from avocado seeds (Fig. 6, compounds 7–11) (Rosenblat *et al.* 2011). *Carotenoids* were found in peels of Hass variety by Ashton *et al.* (2006). These comprise β-carotene, neoxanthin, violaxanthin, zeaxanthin, and α- and β-carotene (Fig. 7). These compounds have a great interest in animal health since carotenoids influence both cellular and humoral immunity, thus these can be used to prevent infectious and inflammatory processes. Furthermore, recent investigations on the role of carotenoids in angiogenesis, apoptosis, and gene regulation, revealed mechanisms of immune system regulation (Pechinskii and Kuregyan 2014). *Polyols* (ascorbic acid, mannoheptulose, and perseitol, among others), were reported by Tesfay *et al.* (2010) in avocado peels and seeds (Figs. 8, 9), and the latter was also found in Hass avocado peels by Figueroa *et al.* (2018). The consumption of such compounds has health effects on young monogastric mammals, which exhibited an increased survival rate, both over the intermediate portions of the pre-weaning period and over the entire pre-weaning period (Rodas *et al.* 2015). Avocado-derived compounds containing polyols, comprising D-mannoheptulose and/or perseitol, have been proposed for treating and preventing innate immunity modification diseases by increasing the

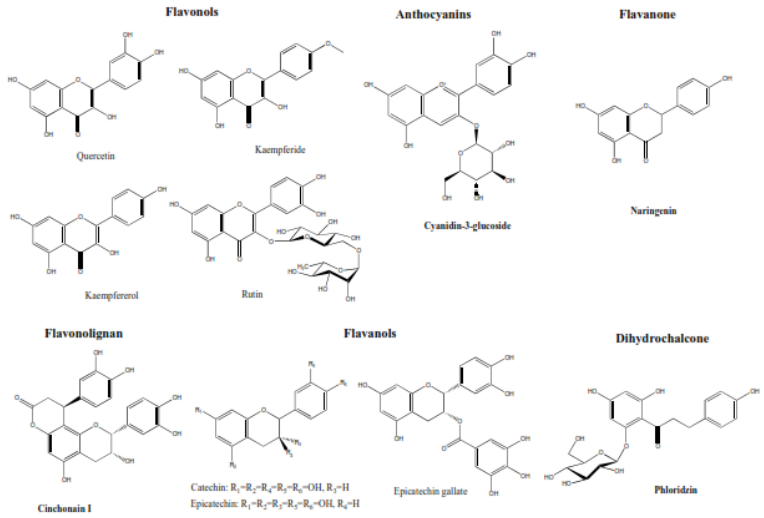

Fig. 3: Flavonoids contained in avocado by-products

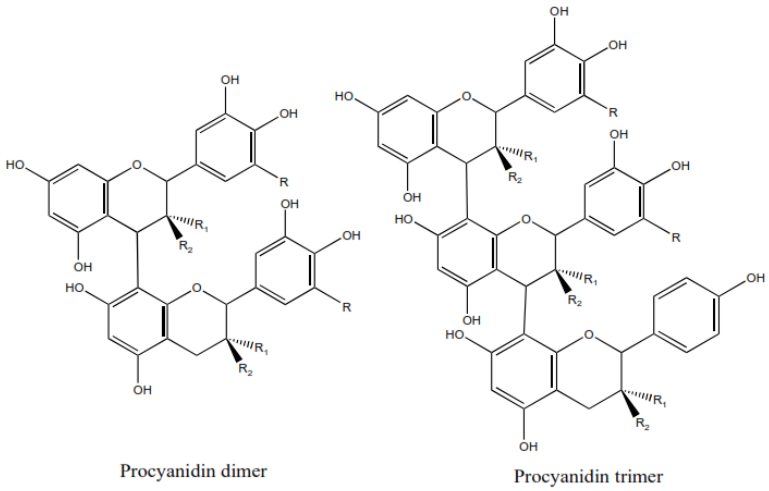

Fig. 4: Procyanidins contained in avocado by-products

production of antimicrobial peptides (*e.g.*, Human β-defensin-2), without inducing inflammatory reactions, irritation, or intolerance (Piccirilli *et al.* 2015). *Sterols* (Fig. 10) occur mainly in the unsaponifiable obtained from the avocado peel, which contains 0.2% of saturated aliphatic hydrocarbons and more than 1% of sterols (Msika *et al.* 2013). This unsaponifiable includes stigmasterol, ß-sitosterol, campesterol, Δ^5-avenasterol, Δ^7-stigmasterol, and citrostadienol. Alkhalf *et al.* (2019) reported in avocado seeds cholesterol, stigmasterol, and β-sitosterol. Sterols-rich by-products could have interest in improving animal health since such compounds positively affect the wellness and health of farm animals through a variety of physiological functions, *e.g.*, antitumor effects, hormone-like actions, oxidation and inflammation resistance, immune modulation, and *in vivo* growth regulation (Guil-Guerrero *et al.* 2016a). Avocado seeds contain a lipid fraction in which occurs some FA as LA, OA, and PA, which store energy, while LA is an essential nutrient and OA is a bioactive compound (Takenaga *et al.* 2008). Besides these, other *organic acids* are present in avocado by-products, which are depicted in Fig. 11. Hass avocado peels contain quinic, citric, malic, and succinic acids (Figueroa *et al.* 2018), while two glycosylated abscisic acid derivates were isolated from seeds (Ramos *et al.* 2004). These molecules have been assayed in abscisic acid-fed mice and typified as healthy, since they decrease blood glucose concentrations in fasting, ameliorate glucose tolerance, adipocyte hypertrophy, tumor necrosis factor-α (TNF-*α*) expression, and macrophage infiltration, which were significantly improved (Guri *et al.* 2007). Therefore, such molecules could have positive health effects on farm animals, although the extent of this effect remains unknown. In addition to all the above-detailed compounds, Figueroa *et al.* (2018) found in avocado peels a lignan (nudiposide) and

Table 1: Total phenolics, anthocyanin, and flavonoids in avocado by-products

Variety	Seed	Peel	Reference
Total phenolics			
Hass, Gwen, Fuerte	16.5-29.8 g GAE·kg^{-1} g FW	-	Torres *et al.* (1987)
-	88.2 g GAE·kg^{-1} DW	-	Soong and Barlow (2004)
Several cultivars	19.2-51.6 g GAE.kg^{-1} FW	4.3-113.9 g GAE·kg^{-1} FW	Wang *et al.* (2010)
Hass	17.0–60.8 g GAE·kg^{-1} g DW	32.9–90.0 g GAE·kg^{-1} g DW	Rodríguez-Carpena *et al.* (2011)
Fuerte	20.3–69.1 g GAE·kg^{-1} DW	40.5–172.2 g GAE kg^{-1} DW	Rodríguez-Carpena *et al.* (2011)
-	7.20 g GAE·kg^{-1} g FW	8.39 g GAE kg^{-1} g FW	Deng *et al.* (2012)
Hass	9.51 g CE·kg^{-1} DW	25.32g CE·kg^{-1} DW	Kosińska *et al.* (2012)
Shepard	13.04 g CE·kg^{-1} DW	15.61 g·CE·kg^{-1} DW	Kosińska *et al.* (2012)
-	292 g GAE·kg^{-1} DW	-	Pahua-Ramos *et al.* (2012)
-	29.37 g GAE·kg^{-1} g DW	30.01 g GAE·kg^{-1} g DW	Oboh (2013)
Hass	57.3 g·GAE·kg^{-1} g DW	63.5 g·GAE kg^{-1} g DW	Daiuto *et al.* (2014)
-	1.553 g GAE·kg^{-1} g DW	12.523 g·GAE kg^{-1} g DW	Morais *et al.* (2015)
Hass	5.7 g GAE·kg^{-1} g DW	19.7 GAE·kg^{-1} g DW	Calderón-Oliver *et al.* (2016)
Hass	72.5 g·kg^{-1}	227 g·kg^{-1}	Melgar *et al.* (2018)
-	12.52-33.23 g GAE·kg^{-1} DW	12.42-31.10 g GAE·kg^{-1} DW	Saavedra *et al.* (2017)
Hass	57.3 g GAE·kg^{-1} DW	63.5 g GAE·kg^{-1} DW	Tremocoldi *et al.* (2018)
Fuerte	59.2 g GAE·kg^{-1}DW	120.3 g GAE·kg^{-1} DW	Tremocoldi *et al.* (2018)
Nariño	328.8 g GAE·kg^{-1} DW	527.8 g GAE·kg^{-1} DW	Rosero *et al.* (2019)
cv. Criollo sp.	0.30g GAE·kg^{-1} g DW	-	Cid-Pérez *et al.* (2021)
Pinkerton	124 GAE·kg^{-1} FW·min^{-1}	352 GAE·kg^{-1} FW·min^{-1}	Skenderidis *et al.* (2021)
Hass and Hass type cv.	-	1.40–18.94 g GAE·kg^{-1} FW	Ramos-Aguilar *et al.* (2021)
Hass	2 mg·kg^{-1} DW	2-9 mg·kg^{-1} DW	Tesfay *et al.* (2010)
Total flavonoids			
-	5.69 mg TE·kg^{-1}	13.60 mg TE·kg^{-1}	Lee *et al.* (2008)
-	2.32 g QE·kg^{-1} g DW	3.39 g QE·kg^{-1} g DW	Oboh (2013)
Hass	2.8 g QE·kg^{-1} DW	10.9 g QE·kg^{-1} DW	Calderón-Oliver *et al.* (2016)
Total tannins			
-	137.2 mg TE·kg^{-1} FW	223.45 mg TE·kg^{-1} FW	Lee *et al.* (2008)
-	-	49 g TE·kg^{-}1 DW Non tannin 10; tanin 39 Condensed tannin 22.1	Negesse *et al*. (2009)
Hass	0.09 g GAE·kg^{-1}g DW	0.04 g GAE·kg^{-1}g DW	Calderón-Oliver *et al.* (2016)
Total anthocyanins			
Hass	-	0-230 g·kg^{-1} FW, as cyanidin 3-O-glucoside	Ashton *et al.* (2006)

Abbreviations: CE: catechin equivalent; DW: dry weight; FW: fresh weight; GAE: gallic acid equivalent; QE: quercetin equivalent; TE: tannic acid equivalent

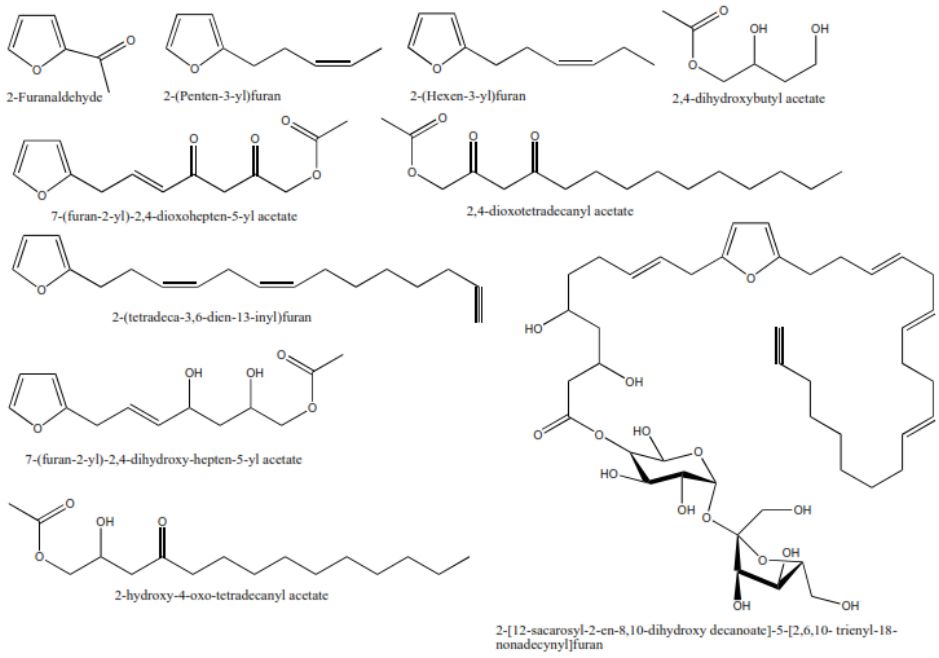

Fig. 5: Furans contained in avocado by-products

Table 2: Phenolic compounds occurrence in avocado by-products

Variety	Seeds	Peels	Reference
Several cultivars	Procyanidins: 23.7-55.6 kg^{-1} FW	Procyanidins 4.9-38.9 g GAE·kg^{-1} FW	Wang *et al.* (2010)
Has	Procyanidins > hydroxycinnamic acids > catechins > hydroxybenzoic acids	procyanidins> hydroxycinnamic acids> catechins	Rodríguez-Carpena *et al.* (2011)
Fuerte	Procyanidins > hydroxycinnamic acids > catechins	Procyanidins > catechins > hydroxycinnamic acids > hydroxybenzoic acids	Rodríguez-Carpena *et al.* (2011)
-	Epicatechin 219.2, gallic acid 52.0 mg·kg^{-1} DW	Catechin 520.8, chlorogenic acid 116.8, homogentisic acid 113.6, cyanidin 3-glucoside 31.6 mg·kg^{-1} DW	Deng *et al.* (2012)
Has	Catechin/epicatechin gallate 152.8, procyanidin trimer A (II) 89.3, procyanidin trimer A (I) 81.7 mg·kg^{-1} DW	Catechin 148.8, procyanidin dimer B (I) 135.4, chlorogenic acid 81.8, quercetin-3-O-arabinosyl-glucoside 80.4 mg·kg^{-1} DW	Kosińska *et al.* (2012)
Shepard	Catechin/epicatechin gallate 105.4, procyanidin trimer A (I) 98.9, procyanidin trimer A (II) 73, 3-O-caffeoylquinic acid 53.5 mg CE·kg^{-1} DW	Quercetin 3-O-galactoside 144.1, quercetin derivative (III) 81.9, quercetin-3-O-arabinoside 94.1, quercetin derivative (I) 63.7 mg CE·kg^{-1} DW	Kosińska *et al.* (2012)
-	Protocatechuic 128.1, kaempferide 107.42, rutin 9.63, vainillic acid 28.67, syringic acid 2.51, kaempferol 2.19, chlorogenic acid 0.516 mg·kg^{-1} DW	-	Pahua-Ramos *et al.* (2012)
-	-	Catechin hydrate 1.71 mg·kg^{-1} DW Epicatechin 1.298 mg·kg^{-1} DW	Morais *et al.* (2015)
Hass	3-O-Caffeoylquinic acid 19 mg, B-type (epi)catechin 12 mg, epicatechin 46.5 mg·kg^{-1} extract	4- and 5-O-Caffeoylquinic acid 40.9, epicatechin 46.5, catechin 20, B-type (epi)catechin 96, quercetin 7 mg·kg^{-1} extract	Melgar *et al.* (2018)
	Catechin 242.6, chlorogenic acid 160.7, caffeic acid 136.9, ferulic acid 0.87 mg·kg^{-1} DW	Chlorogenic acid 1376, p-Coumaric acid 17.4, ferulic acid 50.5 mg·kg^{-1} DW	Saavedra *et al.* (2017)
Hass		*Hydroxybenzoic acids*: benzoic, *p*-hydroxybenzoic protocatechuic, gentisic acids.	Figueroa *et al.* (2018)
	-	*Hydroxycinnamic acids:* caffeic acid, caffeoylquinic acids derivatives, *p*-coumaric acid. *Flavanoids*: naringenin, luteolin 7-O-(2″-O-pentosyl) hexoside, quercetin, quercetin glucosides, kaempferol glucosides, cinchonain I. Procyanidin dimers, trimers and tetramers. *Lignans*: nudiposide.	
Hass	Trans-5-O-caffeoyl-D-quinic acid 1.63 mg·kg^{-1}; Procyanidin B_1 1.52 mg·kg^{-1}; catechin 3.64 μg·mg^{-1}; epicatechin 10.27 mg·kg^{-1} DW	Procyanidin B2 48.38 μg·mg^{-1}, epicatechin 40.21 mg·kg^{-1} DW	Tremocoldi *et al.* (2018)
Fuerte	Trans-5-O-caffeoyl-D-quinicacid 5.74 mg·kg^{-1}; procyanidin B_1 2.27 mg·kg^{-1}; catechin 8.13 mg·kg^{-1}; epicatechin 11.06 mg·kg^{-1} DW	Procyanidin B_2 28.34 mg·kg^{-1}; epicatechin 30.40 mg·kg^{-1} DW	Tremocoldi *et al.* (2018)
Nariño	Flavonols, catechins, hydroxycinnamic acids, quercetin glycosides and procyanidins, phloridzin	Flavonols, catechins, hydroxycinnamic acids, quercetin glycosides, procyanidins, phloridzin	Rosero *et al.* (2019)
Hass and "Hass type"		Chlorogenic acid (0.13-0.91), procyanidin B2 (0.29-5.86), Epicatechin (0.24-2.17), cyanidin 3-O-glucoside (0.09-0.83) g·kg^{-1} FW	Ramos-Aguilar *et al.* (2021)

Abbreviations: DW: dry weight; FW: fresh weight; GAE: gallic acid equivalent; RE: rutin equivalent; TE: tannic acid equivalent; QE: quercetin equivalent

two glucosides: the iridoid-type penstemide, and (1′S, 6′R)-8′-hydroxyabscisic acid β-d-glucoside, as well as hydroxylated FA. *Phytates* were described in avocado peels by Negesse *et al.* (2009). Phytic acid (Fig. 12), is the main storage form of phosphorus (P) in several plant tissues, especially bran and seeds, where it is found as phytate, including Mg, Ca, Na, and K. As phytate form, P is not available to humans and non-ruminant animals because they lack the digestive enzyme phytase, which releases phosphate from the inositol in the phytate molecule. This situation is different from that of ruminants, which can digest phytate with the aid of the phytase that several microorganisms produced in the rumen (Klopfenstein *et al.* 2002). Phytate can form complexes with protein, which are pH-dependent. Such complexes reduce the bioavailability of several mineral elements (Pallauf and Rimbach 1997). However, phytic acid can induce positive actions, for instance through the prevention of the formation of free radicals and by the reduction of the risk of high-fat diet-induced hyperglycemia *via* regulation of hepatic glucose enzyme activities (Kim *et al.* 2010). Phytic acid also decreases plasma triglycerides and cholesterol and induces a change in the carryover of heavy metals (Pallauf and Rimbach 1997).

All the reviewed compounds develop antibacterial, anti-inflammatory, and immunity-promoting actions, so the intake of PA would contribute to improving the health of the digestive tract of farm animals.

Biological activity of avocado by-products

Information on this topic is summarized in Table 4, the selected antimicrobial activity of avocado by-products extracts is detailed in Table 5, while information related to antioxidant properties is described in Table 6.

Antidiabetic, anti-inflammatory, antihepatotoxic, anti-toxic, and antihypertensive

These assays were accomplished through *in vitro* cell cultures and mice models. Uchenna *et al.* (2017), using a murine model demonstrated the effectiveness of raw avocado seeds against hyperglycemia and/or hypercholesteremia, while the seed extracts were characterized as antihypertensive and antihepatotoxic in Wistar rats by Imafidon and Amaechina (2010). Protection against UVB-induced damage and inflammation of the skin was reported by Rosenblat *et al.* (2011), who *in vitro* supplied polyhydroxylated fatty alcohols to keratinocytes from avocado seeds prior to UVB exposure. These

Table 3: Other compounds occurring in avocado by-products

Variety	Seed	Peel	Reference
	Abcisic acid		Ramos *et al*. (2004)
-		-	
Hass		Carotenoids: total: 18-50; lutein: 10-21; *β*-carotene: 5-12; neoxanthin: 2-5 g·kg^{-1} FW. Others: anteraxanthin, violaxanthin, zeaxanthin, α-carotene. Total chlorophylls: 100-210 g·kg^{-1} FW	Ashton *et al*. (2006)
	-		
-	Alkanols, terpenoids, glycosides, furan ring derivatives, and a coumarin.	-	Ding *et al*. (2007)
-	Glycolipids, phospholipids	-	Takenaga *et al*. (2008)
Hass	Ascorbic acid: 12.6-22.7 Mannoheptulose: 5.34-7.95 Perseitol: 0.43-1.62 g·kg^{-1} DW	-	Tesfay *et al.* (2010)
-	-	Phytathe 9 mg TE·kg^{-1} DW	Negesse *et al*. (2009)
Avocado, several cultivars	Total carotenoids 0.7-6.3 mg kg^{-1} FW	Total carotenoids 9.3-17.7 mg kg^{-1} FW	Wang *et al*. (2010)
Ettinger	Hydroxylated fatty alcohols, including persin		Rosenblat *et al*. (2011)
		-	
Hass	Hydroxylated fatty alcohols		Rodríguez-Sánchez *et al*. (2013)
-	1% sterols of unsaponifiable wt	-	Msika *et al*. (2013)
	Sterols: ß-sitosterol, campesterol, stigmasterol, Δ5-avenasterol, Δ7-stigmasterol, citrostadienol	-	
Hass		Organic acids: citric, malic, quinic, succinic. Polyols: perseitol.	Figueroa *et al.* (2018)
	-	Glucosides: Iridoid-type: penstemide; and (1′S, 6′R)-8′-hydroxyabscisic acid *β*-d-glucoside. Hydroxylated fatty acids	
	Fatty acids: mainly, linoleic, oleic and palmitic acids.		Alkhalf *et al.* (2019)
-	Hydrocarbons: C_{18}-C_{30}, squalene. Sterols: cholesterol, stigmasterol and β-sitosterol.	-	
Criollo sp.	Isoprenoids derivates, esters of fatty acids and their derivatives		Cid-Pérez *et al.* (2021)
Hass and Hass type cv.		Polyols, including perseitol and volemitol Organic acids: succinic, citric, malic, quinic, fumaric, oxalic. Sterols: *β*-sitosterol, stigmasterol, campesterol, cycloartenol; *α*- and δ-tocopherols Fatty acids: mainly oleic, linoleic, palmitic *α*- and δ-tocopherols; chlorophylls and pheophorbides; carotenoids (lutein and others)	Ramos-Aguilar *et al.* (2021)

compounds were able to reduce increasing cell viability and enhance DNA repair while decreasing the secretion of PGE2 and IL-6, thus PFA can act as photoprotective agents. Good anti-inflammatory activities of peel and seeds were reported for Hass and Fuerte varieties by Tremocoldi *et al.* (2018), and the main finding was that phenolic compounds-rich peel extracts were able to suppress the release of TNF-*α* and NO. Moreover, gastric ulcer can be prevented by seed extracts. Alkhalf *et al.* (2019) found that avocado peel extract was appropriate to reduce edema in mice at 10 g·kg^{-1} BW, while the prevention of gastric ulcers due to oxidative stress was reported by Athaydes *et al.* (2019), who indicated a reduction of lipid peroxidation and an increasing of superoxide dismutase (SOD) enzyme activity. Anti-toxic and cardioprotective effects of the AE and EE of avocado seeds against doxorubicin (DOX)-induced toxicity were checked in a mice model by Shamlan (2020). Interestingly, avocado extracts mitigated the increased markers of cardiac dysfunction induced by DOX treatment.

Antitumor

These experiments were carried out using both peels and seeds. All trials were accomplished using cancer cell lines cultures, and cell growth inhibition by the MTT test was the more frequent antitumor assay. Alkhalf *et al.* (2019) found inhibition of the growth of hepatocellular and colon cancer cells by the lipid extracts of avocado peels. Dabas *et al.* (2019) checked methanol extracts (ME) for *in vitro* antitumor tests using several human cell lines, and a reduction in the viability of cells was found due to that ME downregulate the expression of cyclin D_1 and E_2, and the nuclear translocation of nuclear factor *κ*B. Vo *et al.* (2019) found that the EE of seeds inhibited cancer cells growth and provided protection against H_2O_2-induced DNA damage and that AVM acts against NO production from cells. All these works concluded that avocado seeds constitute a raw source of healthy compounds and that these extracts can be used as ingredients for functional foods formulations.

Table 4: Biological activity of avocado by-products

Activity	Model	Variety	Extracted	Test	Results	Concluding remarks	Reference
Antidiabetic	Sprague Dawley rats Spontaneous hypertensive rats	-	Raw seeds	Feeding avocado seeds	Avocado seeds lowered blood glucose and cholesterol and enhance liver glycogen storage	Possible uses of avocado seeds against hyperglycemia and/or hypercholesteremia.	Uchenna *et al.* (2017)
Antihepatotoxic	Wistar rats	Fuerte	Seeds AE	NaCl-treated rats	-AE reduce weight gain and blood pressure - AE reduces alkaline phosphatase	AE are antihypertensive and	Imafidon and Amaechina (2010)
Anti-inflammatory	*In vitro* cell cultures	-	Seeds PFA	*In vitro* keratinocytes cultures	Decreased IL-6 and cyclobutane pyrimidine dimers after UV-B radiation	PFA reduce UV-B-induced inflammation in skin	Rosenblat *et al.* (2011)
	Mice model	-	Peels and seeds lipid extracts	Carrageenan-induced edema in mice	Avocado peel extract reduce swelling at 10 $g \cdot kg^{-1}$ of extract	Hydrocarbons, St and UFA have anti-inflammatory properties	Alkhalf *et al.* (2019)
	In vitro cell cultures	Hass and Fuerte	Peels and seeds AE and EE	-Lipopolysaccharides-stimulated macrophages - TNF-α production and MTT	Fuerte peel extract suppressed the release of TNF-α and NO	Phenolics from peels are anti-inflammatory	Tremocoldi *et al.* (2018)
Anti-inflammatory, hepatoprotective, antihypertensive	Mice model	-	Seeds EAE	Indomethacin-induced gastric ulcer in mice	Extract mitigates oxidative stress by reducing lipid peroxidation and increasing superoxide dismutase enzyme activity	Gastric ulcer can be prevented by seed extracts	Athaydes *et al*. (2019)
Anti-toxic and cardioprotective	Mice model: doxorubicin (DOX)-induced toxicity	Avocado	Seeds AE and EE	- DOX and DOX+ AE/EE- treated rats	DOX treatment increased markers of cardiac dysfunction, and avocado extracts mitigated it	-EE more effective than AE, as evidenced by biochemical markers.	Shamlan (2020)
Antitumor	*In vitro* cell cultures	-	Peels and seeds lipid extracts	HCT116 colon- and HePG2 liver-human cell line cultures. MTT test	Seed lipids inhibited hepatocellular and colon cancer cells growth	Seeds lipids have anti-cancer effects	Alkhalf *et al.* (2019)
	In vitro cell cultures	Hass	Seed colored ME	LNCaP cells - MTT test, cell cycle analysis, apoptosis	-Extracts reduced *in vitro* cancer cells viability, downregulated the expression of cyclin D_1 and E_2, associated with G_0/G_1 phase cycle arrest, and nuclear translocation of nuclear factor κB - Extracts induced apoptosis	Extracts can be used as a functional food ingredient	Dabas *et al.* (2019)
Antitumor and antioxidant	*In vitro* free radical scavenging and anti-proliferative activities	-	Seed EE	RAW 264.7 cells - NO production, MTT cancer cell growth inhibition, DNA oxidative assay	-High IC_{50} for free radical scavenging fractions - Seed extract protect against H_2O_2-induced DNA damage - EE reduces NO production from lipopolysaccharide-stimulated cells - Extracts inhibited the proliferation of cancer cells	Avocado seeds are a source of healthy compounds	Vo *et al.* (2019).
Antimicrobial	Antifungal - *Cladosporium cladoposioides*	Avocado	Inmature peels, searching antifungal fractions	-Antifungal activity by TLC bioassay -Incubation of compounds with fungi	Trihydroxy fragments could be present in all active compounds	Preventive effects against avocado anthracnose	Adikaram *et al.* (1992)
	Antiprotozoal - *Trypanosoma cruzi*	Avocado	Seeds, EE, including six	*In vitro T. cruzi* immobilization	PFA showed moderate activity against epimastigotes and trypornastigotes	PFA prevent *T. cruzi* disease, Chagas'	Abe *et al.* (2005)
	Amoebicidal, Giardicidal Trichomonicidal Antimycobacterial	Avocado	Seeds, CE and EE	*In vitro* cell cultures	- CE and EE activity against *E. histolytica*, *G. lamblia* and *T. vaginalis* (IC_{50} <0.634 $\mu g \cdot ml^{-1}$). - CE inhibited *M. tuberculosis* reference	Extracts active against all tested microorganisms	Jiménez-Arellanes *et al*. (2013)
	Antifungal -*Candida* spp., *Cryptococcus neoformans, Malassezia pachydermatis*	Avocado	Seeds HE and EE	Antifungal activity by microdilution in RPMI	Extracts active against all the yeast strains tested *in vitro*, with differing MIC	Candidates as antifungal agents	Leite *et al*. (2009)
	Antibacterial and antifungal	Avocado	Seeds ME and EAE	Disc diffusion method	ME and EAE had the lowest MIC against *C. albicans*	EA and EAE had higher activity than treptomycin	Idris *et al.* (2009)
	Antibacterial and antifungal	Hass' and 'Fuerte'	Peel, pulp, and seed extracts	Disk diffusion method	-Gram-positive bacteria more sensitive than Gram-negative. - Gram-positive *Bacillus cereus* and *Listeria monocytogenes* more sensitive - *E. coli* was the most sensitive Gram-	Good antimicrobial properties	Rodríguez-Carpena *et al.* (2011)
	Antibacterial	Avocado	Seeds: AE, ME and EE	Disk diffusion method	Seed extracts active against *S. aureus* and *B. subtilis.*	Seeds have highly antibacterial activity	Nagaraj *et al.* (20 10)
	Antibacterial	Fuerte, Hass, Shepard	Seeds and epicarp: AE and EE	Hole plate method	-Effect of ethanol extracts toward bacteria -AE activity only for *Listeria monocytogenes* (93.8–375.0 $\mu g \cdot mL^{-1}$) and *Staphylococcus epidermidis* (354.2 $\mu g \cdot mL^{-1}$)	Antimicrobial against *S. enteritidis*, *Citrobacter freudii*, *P. areuginosa*, and *Enterobacter*	Chia and Dykes (2010)

Table 4: Continued

Table 4: Continued

	Clostridium sporogenes vegetative cells and active endospores	Hass	Seeds AcE	Disk diffusion method	-All extracts inhibited vegetative cells and active endospores -MIC of molecules 7.8-15.6 μg·mL^{-1} -Bactericidal for enriched fraction at 19.5 μg·mL^{-1}	Identified molecules inhibit Gram-positive spore-forming bacteria.	Rodríguez-Sánchez *et al.* (2013)
	Antimicrobial and antioxidant	Hass	- Seed and peel AE -Nisin, antimicrobial peptide	-Antimicrobial activity by turbidimetry *-Listeria innocua*, *E. coli*, *Lactobacillus sakei*, *Weissella viridescens*, and *Leuconostoc mesenteroides*.	- Polyphenols from peel extracts have antioxidant and radical scavenging properties - Peel and seed extracts and nisin have synergic antimicrobial properties	Avocado peel + nisin reduce the amount of nisin to achieve antioxidant and antimicrobial effects	Calderón-Oliver *et al*. (2016)
	Antioxidant, antimicrobial	Hass	Seed and peels AE and EE	- MIC, MBC, and MFC	- Bactericidal effects in Gram positive and negative strains. - Extracts from seeds displayed better MCB than peels - Fungicidal effect in 2 strains for	-High activity against some bacteria and fungi strains	Melgar *et al.* (2018)
Larvicidal	*Artemia salina* and third stage *Aedes aegypti* larvae	Avocado	Seeds HE and ME	-Toxicity tests using *A. salina* -Larvicidal in *A. agypti*	Extracts active against larvae	Alternative dengue control agents	Leite *et al.* (2009)
Radioprotective	Sprague-Dawely rats	Avocado	Peel extracts	Exposition to 6 MV X-Ray	Avocado peel extract induced a greater recovery of lymphocytes, red blood cells, and platelets to irradiate rats when compared to rats without peel extract administration. SOD was further	Avocado peel extract acts as a radiation protective agent for blood cells and major organs	Kim *et al.* (2020)
Toxic	Acute and sub-acute toxicity in rats	Avocado	Seeds, EAE extract	- IP administration of seed extract - IP subacute toxicity for 14 d at 75 and 150 mg·kg^{-1}	-Acute toxicity study showed low LD_{50} - Liver and kidney had normal architecture after 14 d exposure -14 d-treatment decreased food consumption, BW, and blood	Seed EAE had medium toxicity	Taha *et al*. (2008)
	Toxicity in rats	Avocado	Seeds, AE	- LD_{50} and mortality - Sub-acute experiments, doses at a quarter of the maximum dose (10 mg·kg^{-1} BW)	- Hematological parameters and ALT, AST, albumin and creatinine not significantly altered.	The seed extract was safe on acute and sub-acute basis	Ozolua *et al.* (2009)
	Oral acute toxicity in mice	Avocado	Seeds AE and ME	-Hypolipidemic test - LD_{50} of seeds -Antioxidant -Oral Acute	-100% mortality after 6 d in the group fed with 2500 mg seeds·kg^{-1} BW -125 mg AS·kg^{-1} BW reduced the elevated levels of total cholesterol	AE and ME can be used for treating hyperlipidemia	Pahua-Ramos *et al*. (2012)
	-Acute toxicity test in BALB/c mice -Genotoxicity	Avocado	Seed EE	-LD_{50} -Genotoxicological study - Erythrocyte micronucleus test	-LD_{50} EE: 1200.75 mg·kg^{-1} BW -EE at 250 mg·kg^{-1} BW inhibited micronucleus formation	- EE induces acute toxicity at 500 mg·kg^{-1} - EE lacks mutagenic effects on blood cells	Padilla-Camberos *et al.* (2013)
	Wistar Albino Rats: -Hepatotoxicity -Liver enzymatic activity	*P. americana* seeds	Seed phenolics AE and EE	AST, ALT, and ALP activities	Hepatotoxic effect after oral administration of phenolic AE	- Liver damage - AE is hepatotoxic	Umar *et al.* (2016)

Abbreviations. AE: aqueous extract; AcE: acetone extract; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; BW: body weight; CE: chloroform extract; EAE: ethyl acetate extract; EE: ethanol extract; HE: hexane extract; IP: intraperitoneal; MBC minimum bactericidal concentrations, MFC: minimum fungicidal concentrations; ME: methanol extract; MIC: minimum inhibitory concentrations; PFA: polyhydroxylated fatty alcohols; RPMI: Roswell Park Memorial Institute; SOD: superoxide dismutase; St: sterols; UFA: unsaturated fatty acids

Antimicrobial

Information on this activity is summarized in Table 4, and selected data on MIC (mg·mL^{-1}) and inhibition zone (mm) at 100 mg·mL^{-1} are displayed in Table 5. The most widely used method to check the antimicrobial activity of AP extracts was the agar disk technique, although the hole plate method and turbidimetry were also used. Jiménez-Arellanes *et al.* (2013) tested chloroform extract (CE) and EE of avocado seeds against *Giardia lamblia*, *Entamoeba histolytica*, and *Trichomonas vaginalis*, and amoebicidal, giardicidal, trichomonicidal, and antimycobacterial activities were found. The trypanocidal effects of ME of seeds against *Trypanosoma cruzi* were checked by Abe *et al.* (2005), and six hydroxylated fatty alcohols, *i.e.*, acetogenins, were the bioactive compounds identified as responsible for such actions. These showed moderate activity against epimastigotes and trypomastigotes and thus can prevent *T. cruzi* disease, the etiological agent for Chagas' illness. Leite *et al.* (2009) checked the *in vitro* antifungal activity of avocado seeds against *Cryptococcus neoformans*, *Candida* spp., and *Malassezia pachydermatis* strains. The authors concluded that the extracts obtained from avocado seeds can be used as dengue control agents.

Several authors tested AP extracts against different pathogenic fungi: Adikaram *et al.* (1992) reported that dichloromethane extract of peels exercised antifungal activity against *Cladosporium cladoposioides*. Such activity

Table 5: Selected antimicrobial activity of extracts of avocado by-products

Variety / extract	*Bacillus cereus*	*Bacillus subtilis*	*Listeria monocytogenes*	*Staphylococcus aureus*	*Staphylococcus epidermidis*	*Streptococcus pyogenes*	*Escherichia coli*	*Klebsiella pneumoniae*	*Pseudomonas aeruginosa*	*Pseudomonas* spp.	*Salmonella typhimurium*	*Mycobacterium avium*	*Yarrowia lipolytica*	Reference
MIC (mg·mL^{-1})														
Seed, ethyl acetate extract [a]	-	20	-	20	-	0	0	0	0	3	0	4		Idris *et al*. (2009)
Seeds, water extract	-	-	09	.	-	0				-		-		Chia and Dykes (2010)
Seeds, ethanol extract	-	-		-	-	.35	-			-		-	.1	Jiménez-Arellanes *et al.* (2013)
Seeds, chloroform extract	-	-		-	-		-			-		-	.02	Jiménez-Arellanes *et al.* (2013)
Chloramphenicol	-	-	40	2	70	-	0	0	0		0	6		Sreedevi and Pradeep (2016)
Peel, ethanol:water, (80:20 v/v)	0	-		0	0.03	-		.30		0		0		Melgar *et al*. (2018)
	.015		.030	0					.030		.10			
Seeds, ethanol:water, (80:20 v/v)	0	-		0	0.03	-		.15		0		0		Melgar *et al*. (2018)
	.020		.030	0					.030		.030			
Streptomycin	0	-		0	0.04	-		.20		0		0		Melgar *et al*. (2018)
	.10		.20						.20		.25			
Inhibition zone (mm) at 100 mg·mL^{-1}														
Seed, ethyl acetate extract[a]	-	32	-	37	-	5	6	7	2	2	6	1		Idris *et al.* (2009)
Seed, methyl alcohol-water	-	16.7	-	20.8	-					-		-		Nagaraj *et al.* (2010)
	-32.7		-30.5											
Peel / Hass	-	-	5	5.80	-		.73			.73		-	.00	Rodríguez-Carpena *et al.* (2011)
			.07											
Seed / Hass	9	-	9	8.33	-					-		-		Rodríguez-Carpena *et al*. (2011)
	.20		.27											
Peel / Fuerte	6	-	5	5.33	-					-		-		Rodríguez-Carpena *et al*. (2011)
	.33		.80							.73			.53	
Seed / Fuerte	7	-	7	6.80	-					-		-		Rodríguez-Carpena *et al.* (2011)
	.87		.33				.67						.20	
Chloramphenicol	2	-	2	19.0	-					-		-		Rodríguez-Carpena *et al*. (2011)
	0.0		1.20	3			1.67			.53				
Chloramphenicol	-	35.6	-	34.0	-					-		-		Nagaraj *et al.* (2010)

[a] Extract displaying more potency among five different-polarity ones

was attributed to trihydroxy fragments, which later were identified as hydroxylated fatty alcohols. Idris *et al.* (2009) tested the activity of ethyl acetate extract (EAE), CE, and ME, which were compared favorably with the activity of the standard streptomycin, while ME and EAE had the lowest MIC value (10 mg·mL^{-1}) against *C. albicans*.

Nagaraj *et al.* (2010) tested several seed extracts against some bacterial pathogens, such as *Bacillus subtilis*, which causes foodborne illness, and *S. aureus*, the causative agent of impetigo, cellulitis, and scalded skin syndrome, being such potential diseases for humans easily transmitted by food animals. Authors assayed AE, EA, ME, and CE against the two above indicated bacteria, and significant activity was found. Chia and Dykes (2010) tested the antimicrobial activity of EA and AA of epicarps and seeds of several avocado varieties. The EA showed antimicrobial activity (0.104–0.417 mg·mL^{-1}) against Gram-positive and Gram-negative bacteria (except for *E. coli*), while AE was only active against *Listeria monocytogenes* and *Staphylococcus epidermidis*. No inhibition by either EA and AA were observed against *Aspergillus flavus* and *Penicillium* spp. Rodríguez-Carpena *et al.* (2011) found highly antibacterial activity for AP against several pathogens and spoilage microorganisms commonly found in meat products. The authors found Gram-negative bacteria less sensitive than Gram-positive, as demonstrated by the measured inhibition zone (mm) at 100 mg·mL^{-1}. Rodríguez-Sánchez *et al.* (2013) screened the AE of seeds, further fractionated, against active endospores and vegetative cells of *Clostridium sporogenes*. Authors performed bioassay-guided purification of crude extracts from seeds, based on inhibitory properties, and linked antimicrobial activity to six acetogenin compounds (Fig. 6, compounds 1–6). Both vegetative cells and active endospores were inhibited by the extracts, and the MIC of isolated molecules was found in the 7.8 to 15.6

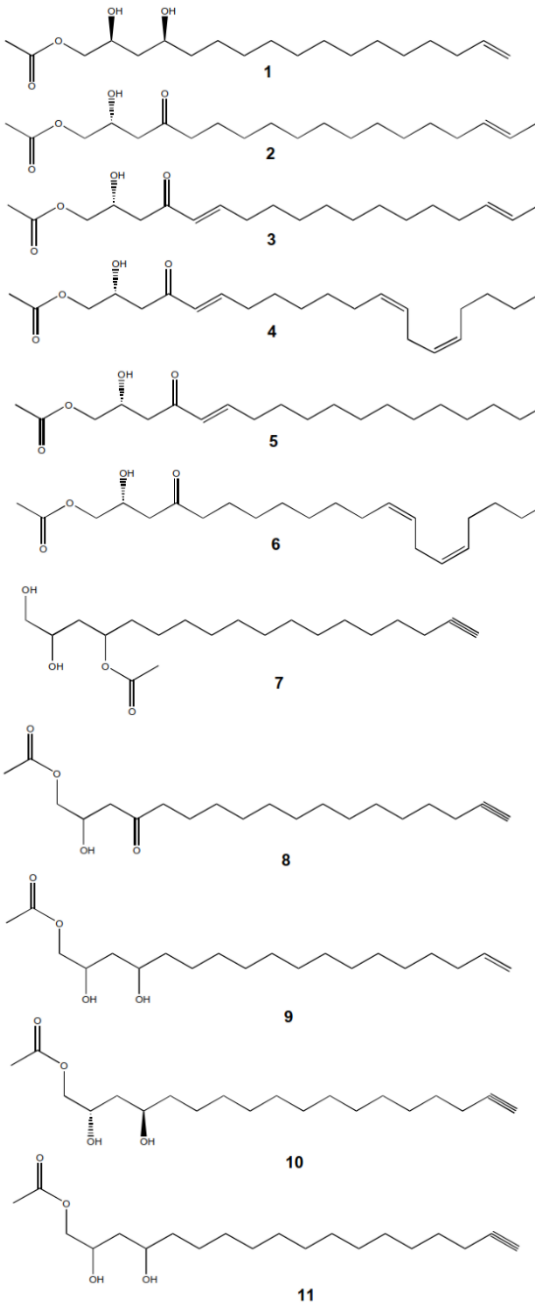

Fig. 6: Chemical structures of acetogenins identified in avocado by-products. Active compounds 1−6 isolated from an avocado seed extract capable of inhibiting *Clostridium sporogenes* PA 3679 (ATCC 7955) vegetative cell growth and endospore germination. 1, (2S,4S)-1-acetoxy-2,4-dihydroxy-n-heptadeca-16-ene;2, persediene; 3, persenone-C; 4, persenone-A; 5, persenone-B; 6, persin (Rodríguez-Sánchez *et al*. 2013). Compounds 7-11 are anti-inflammatory, as described by Rosenblat *et al*. (2011)

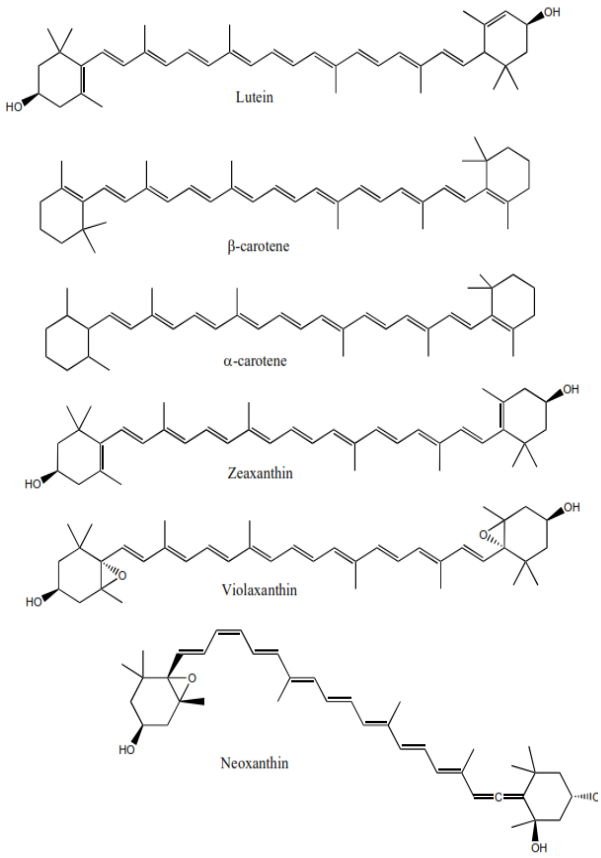

Fig. 7: Chemical structures of carotenoids contained in avocado by-products

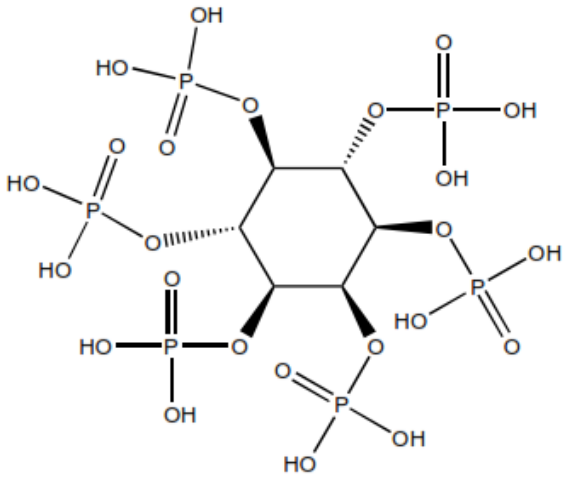

Fig. 8: Chemical structure of phytic acid identified in avocado by-products

μg·mL^{-1} range, while an enriched fraction at 19.5 μg·mL^{-1} showed bactericidal activity. The authors concluded that the isolated compounds should be used as natural alternatives to antibiotics and additives used by the food and pharmaceutical industries to inhibit Gram-positive spore-forming bacteria.

Nisin (an antimicrobial peptide) was assayed in combination with AP extracts to improve the antimicrobial activity against some food-borne bacteria such as *Listeria*,

Table 6: Selected antioxidant activities reported for avocado by-products

Variety	Organ	Antioxidant assays							
		ABTS radical μmol Trolox·g^{-1}	CUPRAC μmol Trolox·g^{-1}	DPPH IC_{50} μg·mL^{-1}	DPPH μmol Trolox·g^{-1}	FRAP μmol $FeSO_4$ g^{-1}	ORAC μmol Trolox·g^{-1}	TEAC μmol Trolox·g^{-1}	Reference
Avocado	Seed FW	236							Soong and Barlow (2004)
Avocado	Seed DW	725				1484			Soong and Barlow (2004)
Avocado	Seed DW	1571-1888				27287-3078			Soong and Barlow (2004)
Avocado	Peel DW			3.83					Lee *et al.* (2008)
Avocado	Seed DW			7.78					Lee *et al.* (2008)
Several cultivars	Seed FW				38-190		58.2-631		Wang *et al.* (2010)
Several cultivars	Seed FW				128-240		229-464		Wang *et al.* (2010)
Hass	Peel DW	1457				1457			Tesfay *et al.* (2010)
Hass	Seed DW	2593				1331			Tesfay *et al.* (2010)
Fuerte	Peel FW	35-242	104-456		35-175				Rodríguez-Carpena *et al.* (2011)
Fuerte	Seed FW	38-195	96-353		28-167				Rodríguez-Carpena *et al.* (2011)
Hass	Peel FW	16-104	56-218		18-89				Rodríguez-Carpena *et al.* (2011)
Hass	Seed FW	22-158	58-275		18-66				Rodríguez-Carpena *et al.* (2011)
Avocado	Peel DW	23.8						34.72	Deng *et al.* (2012)
Avocado	Seed DW	17.5						42.63	Deng *et al.* (2012)
Hass	Peel DW						470.0	161.0	Kosińska *et al.* (2012)
Hass	Seed DW						210.0	94.0	Kosińska *et al.* (2012)
Shepard	Peel DW						290.0	112.0	Kosińska *et al.* (2012)
Shepard	Seed DW						350.0	91.0	Kosińska *et al.* (2012)
Avocado	Seed DW	173.3							Pahua-Ramos *et al.* (2012)
Hass	Peel DW	792			310				Daiuto *et al.* (2014)
Hass	Seed DW	646			411				Daiuto *et al.* (2014)
Avocado	Peel DW			370.22		27.82			Morais *et al.* (2015)
Avocado	Seed DW			46.47		23.71			Morais *et al.* (2015)
Avocado	Peel FW				16.10	9.56 [a]			Rotta *et al.* (2015)
Avocado	Peel DW				763.02	422.8 [a]			Rotta *et al.* (2015)
Hass	Peel DW						216.8		Calderón-Oliver *et al.* (2016)
Hass	Seed DW						1.6		Calderón-Oliver *et al.* (2016)
Hass	Peel DW						12.41-31.10		Saavedra *et al.* (2017)
Hass	Seed DW						8.26-11.01		Saavedra *et al.* (2017)
Fuerte	Peel DW	1004.5			420.5	1881.4			Tremocoldi *et al.* (2018)
Fuerte	Seed DW	580.8			464.9	931.7			Tremocoldi *et al.* (2018)
Hass	Peel, DW	791.5			310	1175.1			Tremocoldi *et al.* (2018)
Hass	Seed DW	645.8			410.7	656.9			Tremocoldi *et al.* (2018)
Nariño	Peel DW			138.2				5,700	Rosero *et al.* (2019)
Nariño	Seed DW			320.1				3,200	Rosero *et al.* (2019)
Hass, Hass type	Peel FW							6.99-103.12	Ramos-Aguilar *et al.* (2021)
Ascorbic acid		8138.86	3009.68		54189.92				Tusevski *et al.* (2014)
α-tocopherol		2685.04	2488.81		2221.83				Tusevski *et al.* (2014)
BHA		2476.47	6422.31		4317.85				Tusevski *et al.* (2014)

[a] expressed as $Fe_2SO_4.7H_2O$

Abbreviations: ABTS: 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid; CUPRAC: cupric reducing antioxidant capacity; DW: dry weight; DPPH: 2,2-diphenyl-1-picrylhydrazyl; FW: fresh weight; FRAP: Ferric Reducing Antioxidant Power; ORAC: Oxygen Radical Absorbance Capacity; TEAC: trolox equivalent antioxidant capacity

as well as the antioxidant capacity (Calderón-Oliver *et al.* 2016). Both peel and seed extracts-containing mixtures showed antioxidant activity and radical scavenging capacity, which was attributed to their polyphenolic composition, and a synergic antimicrobial response was noted in the mixtures of both extracts in conjunction whit nisin. The highest antimicrobial and antioxidant activities were obtained for a mixture containing 61% of peel extract with 39% of nisin. Later, the encapsulation of a mixture of nisin and avocado peel extract by freeze and spray drying was optimized. The authors concluded that such microcapsules could be used as functional ingredients (Calderón-Oliver *et al.* 2017).

The antimicrobial activity measured as MIC and diameters of growth inhibition zones (mm) of AP extracts is compared with that of chloramphenicol in Table 5. Chia and Dykes (2010) and Jiménez-Arellanes *et al.* (2013) found extreme potency for all AP extracts. Idris *et al.* (2009), found higher activity developed by AP against some pathogenic bacteria than that showed by chloramphenicol, as demonstrated by MIC methodology. Concerning the activity evaluated by the diameter inhibition area methodology, Nagaraj *et al.* (2010) found growth inhibitory activity of avocado seed extracts against *B. subtilis* and *S. aureus*, which was similar to that exercised by chloramphenicol and approximately ~4–6 times higher than that found by other authors for *S. aureus*. Melgar *et al.* (2018) found a high capacity of EA of AP against several bacterial and fungal strains. MIC, Minimum Fungicidal Concentration (MFC), and Minimum Bactericidal Concentration (MBC) were checked for 4 Gram-positive, 4 Gram-negative bacteria, and

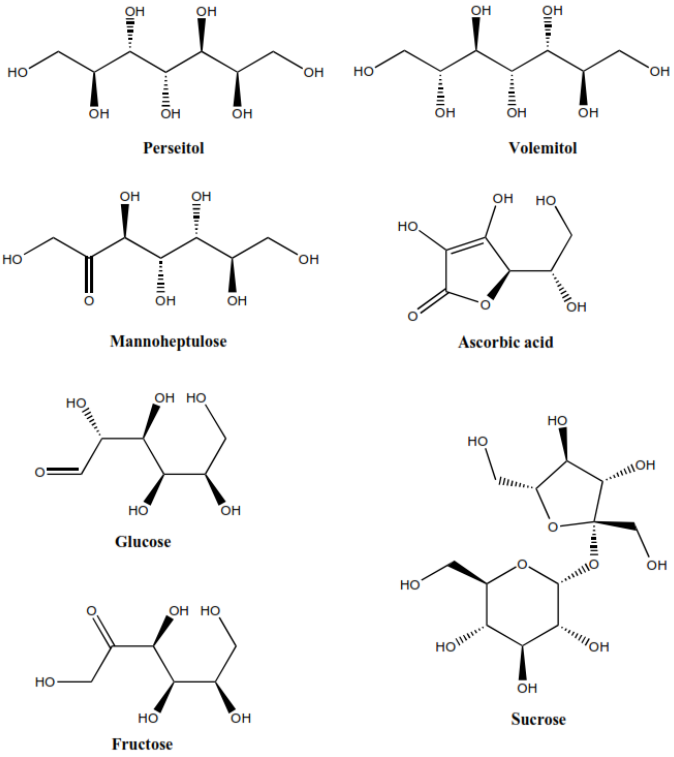

Fig. 9: Chemical structures of polyols identified in avocado by-products

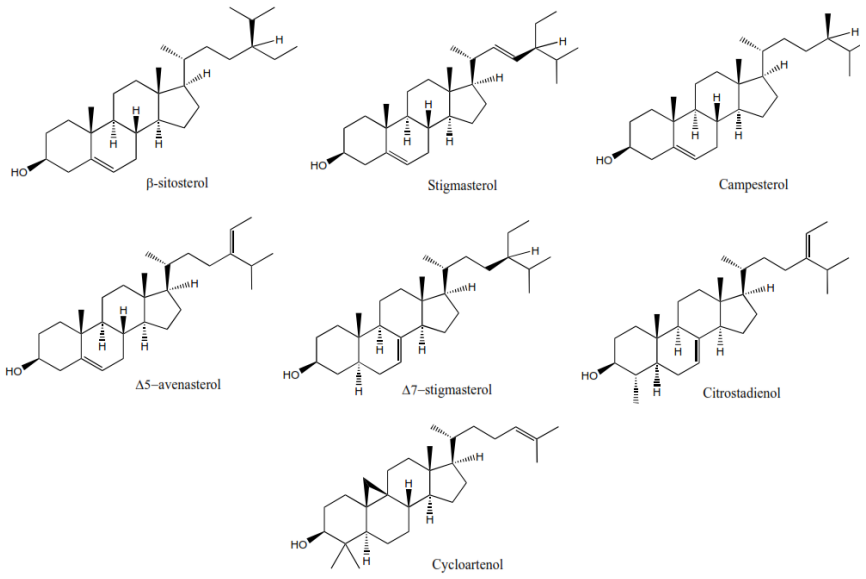

Fig. 10: Chemical structures of sterols identified in avocado by-products

7 microfungi. The activity was found in 7 bacterial strains, and the seeds extracts showed better MBC than peel extracts in 6 out of 8 strains, while the fungicidal effect was exercised only by seeds extracts against some strains.

Differences in antimicrobial activities of AP found by different authors could be related to diverse extraction procedures of AP, bacterial strains assayed or can be due to the various methodologies used for testing bacterial inhibition. In any case, all results indicate high antibacterial activity for avocado peel and seed extracts.

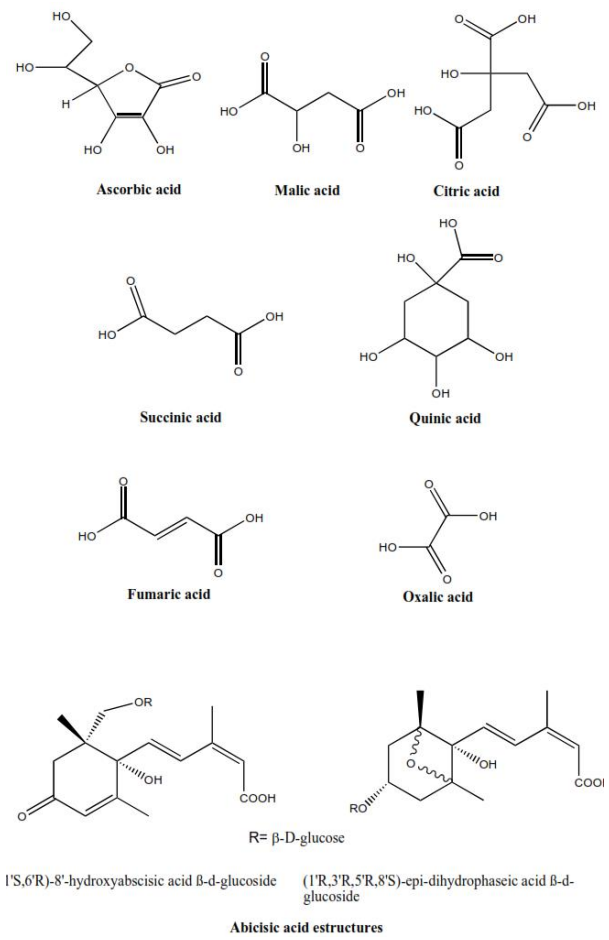

Fig. 11: Organic acids identified in avocado by-products

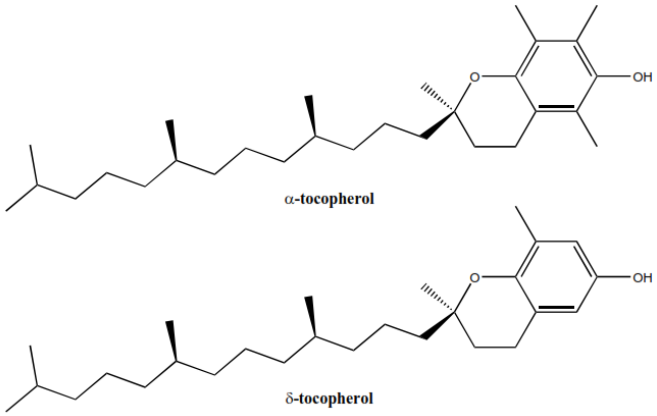

Fig. 12: Tocopherols identified in avocado by-products

Larvicidal activity

Leite *et al.* (2009) tested HE and EE of avocado seeds against *Artemia salina* and evaluated larvicidal activity against *Aedes aegypti*. They concluded that the extracts obtained from avocado seeds merit further research to be used against dengue.

Toxicity of avocado by-products

Several experiments were performed to determine the potential toxicity of avocado seeds, which was mainly attributed to perseitol occurrence. Acute and sub-acute toxicity in rats was determined by intraperitoneal (i.p.) administration of EAE of avocado seeds (Taha *et al.* 2008).

At the end of a 14 d-trial, it was found that the liver and kidney showed normal architecture and that the treatment decreased food consumption, BW, and blood parameters, concluding that the EAE induced relatively low toxicity. Another experiment was performed on rats to assess the possible toxicity of the AE of seeds (Ozolua *et al.* 2009). The authors calculated LD_{50} and found that hematological parameters and the levels of albumin, creatinine, alanine aminotransferase (ALT), and aspartate Aminotransferase (AST), remained unchanged. Moreover, the seed extract was found to be safe on an acute and sub-acute basis. Pahua-Ramos *et al.* (2012) performed oral acute toxicity assays in mice-feed avocado seeds. They found hypolipidemic and antioxidant effects while feeding with 2.5 g of avocado seeds·kg^{-1} BW for 6 d induced a 100% of mortality; however, it was noted that125 mg of avocado seeds·kg^{-1} BW reduced the elevated levels of total cholesterol. Thus, it was concluded that both AS and ME or avocado seed flour can be used for treating hyperlipidemia. Padilla-Camberos *et al.* (2013) performed an acute toxicity test in male BALB/c mice, obtaining an LD_{50} for the seed extract of 1200.75 mg·kg^{-1}. It was found that 250 mg·kg^{-1} of extract and the negative control induced a low amount of micronucleated cells; however, *in vivo* mutagenicity on peripheral blood cells after seed extract supplementation was not observed. Umar *et al.* (2016) assayed hepatotoxic effects of AE and PE of avocado seed on liver enzymatic activity. They found that a daily oral administration of both AE and PE of seeds during 3 weeks at 500 mg·kg^{-1} BW showed hepatotoxic effects. Such actions were also tested for liver enzymes by checking AST, ALT, and alkaline phosphatase (ALP) activities. It was found that a daily oral administration of AE and PE of seeds for 3 weeks at 0.5 g·kg^{-1} induced minor liver damage.

As seen, most experimentation showed weak toxicological effects, which occur only at high doses of seed extracts. Moreover, all experiments were conducted using mice and rats, which can be useful to discern the possible toxicity of AP for humans; however, other animal models designed to evaluate possible toxicity for farm animals remain poorly developed. This deprives knowing the precise use of such by-products to feed farm animals and given the appropriate nutrient composition and phytochemical profiles of AP, further experimentation on this subject is necessary.

Antioxidant activity

Oxidative stress has been cited as responsible for early events conducting to the development of important infectious diseases in farm animals, such as pneumonia and enteritis. Given that oxidative stress should be easily prevented with antioxidants, the use of antioxidant-rich feeds could be a positive action in farm animals (Lykkesfeldt and Svendsen 2007).

This capacity is usually determined through *in vitro* studies. But Oboh (2013) tested several phenolic extracts of different avocado organs in rat's pancreas through a Fe^{2+} induced lipid peroxidation test. All the extracts caused a significant decrease in malondialdehyde contents in the pancreas in a dose-dependent manner, and the seed had the highest inhibitory effect on Fe^{2+} induced lipid peroxidation (IC_{50} = 60.61 μg·mL^{-1}). The authors concluded that the phenolic extracts of several AP were able for protecting the pancreas from *in vitro* lipid peroxidation. This action was attributed to phenolics, due to their reducing power, Fe^{2+} chelating, and radical scavenging abilities.

In vitro performed colorimetric and fluorometric antioxidant capacity tests are based on Hydrogen Atom Transfer (HAT) mechanism. Usually, HAT-based methods monitor competitive reaction kinetics. These methods generally used a synthetic-free radical generator, *e.g*., the 2,2′-azinobis (3-ethylbenzothiazolline-6-sulfonic acid (ABTS). Generally, the antioxidant capacity usually checks the ability of the antioxidants in controlling the degree of oxidation, and the antioxidant capacity tests can be based on the peroxyl radical scavenging, such as those based on the total radical trapping antioxidant parameter (TRAP); oxygen radical absorbance capacity (ORAC); metal-reducing power such as ferric reducing/antioxidant power (FRAP); hydroxyl radical scavenging such as deoxyribose assay; organic radical scavenging such as ABTS, and 2,2-diphenyl-1-picrylhydrazyl (DPPH); and cupric reducing/antioxidant power (CUPRAC) (Karadag *et al*. 2009).

The results of the antioxidant activities of AP compared to ascorbic acid, α-tocopherol, and butylated hydroxyanisole (BHA) checked by various methodologies are displayed in Table 6. Notice that the results obtained for the antioxidant potential of the various extracts of seeds and peels for the same test are quite variable. This variability could be related to the use of by-products from different avocado varieties, and obtained from fruits in different maturation stages and cultivated following different agronomic protocols and under various climates. Good antioxidant activity was found in most of the extracts, albeit with many fluctuations, at about a tenth of that showed by checked pure molecules, *i.e*., ascorbic acid, α-tocopherol, and BHA. The antioxidant activity detected in both peels and seeds was found to be dependent on the type of test performed. For instance, Tesfay *et al.* (2010) found by the ABTS test higher antioxidant capacity for seeds than for peels; however, by the FRAP test the results were the opposite. On the other hand, an increase in the antioxidant capacity was detected in dried seeds and peels in comparison with fresh by-products. In this regard, Rotta *et al.* (2015) indicated an increase of up to 100 times this capacity for dried seeds, which is in good agreement with the findings of Soong and Barlow (2004), who reported that this phenomenon could be related to the production of Maillard-type antioxidants, although several other natural lipophilic antioxidants could have been degraded by drying. In addition, the surplus of the antioxidant activity might be related to the formation of polyphenols. As shown in Table

6, all tests indicate that both avocado peels and seeds have good antioxidant activities, which can be useful for increasing the health of farm animals.

Use of avocado by-products for feeding farm animals

Avocado has been cited as conditionally toxic for some animals, however ill effects of AP seem to be animal species-dependent, and healthy actions by feeding with AP have been found in some animals, such as pigs. The entire avocado fruits are commonly used as feed for pigs because of their high digestibility. However, it has been reported that the whole avocado fruit as pig feedstuff has lower nutritional value than the pulp and that the nutritive value of fruits varies according to cultivar. The seeds have higher nutritive value than peels, as evaluated in pigs by the mobile nylon bag technique (Carmenatti *et al.* 2015). The protein concentrations were found to be higher in pulps and peels than in the seeds of avocado varieties; however, the whole avocado fruit is easily digestible, and therefore fruit discards could be used for feeding pigs, although protein supplementation would be needed when AP constitute an important portion of pig diets (Ly *et al.* 2021). Overall, AP develop health actions in the muscles of pigs: it improves the FA composition, oxidation state and color stability of meat, and the composition of intramuscular fat. Also, the consumption of such by-products increases the degree of fat unsaturation, while the color of the muscles of pigs is better preserved from oxidation (Hernández-López *et al.* 2016). Positive results when feeding pigs with avocado peels were obtained also in rural Busia District, Kenya, by Mutua *et al.* (2012).

AP have been used successfully to feed ruminants. To this end, it has been proposed the avocado meal, which is an oil-extracted by-product from avocado fruits lacking commercial value, which contains high amounts of fiber. Given the high degradability of its dry matter, this AP has been proposed for ruminant diets (Skenjana *et al.* 2006). Generally, AP have been positively evaluated for feeding goats and sheep. For instance, it has been observed that a mix of avocado seeds and orange peels meal, in a 25:35 ratio, has the potential to positively replace guinea grass in the diet of West African Dwarf male growing sheep (Okoruwa *et al.* 2015). Moreover, a trial using avocado waste (a mixture of pulp and peels) included in multi-nutrient blocks for feeding goats was successfully conducted by Evan *et al.* (2020). These workers found an improvement in the quality of the FA profile of milk, while milk yield was unaffected. Authors reported that the intake of multi-nutrient blocks containing 14.8% AP was low, probably due to the oxidation and rancidity of avocado lipids. Interestingly, no changes were noted in milk production, however, feeding blocks with AP increased milk fat content with minor changes in the FA profile of fat milk.

In aquaculture, the use of AP is highly recommended. These can constitute an energy source in fish farms, which are highly dependent on local resources. This assumption was made mainly based on the contents of crude protein and fat, and also considering the effectiveness of removing anti-nutritional constituents (Kassahun *et al.* 2012). In this regard, the antioxidant properties of a tilapia (*Oreochromis niloticus*) diet with the inclusion of AP were evaluated. An increasing pattern was observed for both the antioxidant activity and the total phenolic compounds content as the level of AP inclusion increased. Therefore, AP was considered a good fed ingredient in aquaculture diets because of their antioxidant properties and the added value granted by its use (Jiménez-Ruiz *et al.* 2019).

In birds, the results appear to be contradictory. In this way, it was investigated the effectiveness of avocado seed powder-based supplements on meat quality and the liver and kidney physiology of culled female quails (*Coturnix coturnix japonica*). The results of the experimentation showed that avocado seed powder-containing supplements significantly improved the level of serum glutamic pyruvate transaminase (GPT), creatinine, urea, fat, protein, cholesterol, meat tenderness, and cooking loss. Thus, avocado seed powder-containing supplements improved meat quality and the liver and kidney physiology of the culled female quail (Tugiyanti *et al.* 2019). Similarly, Akinduro *et al.* (2021), proposed the use of avocado seed powder in broiler chicken diets. Authors demonstrated that avocado seed powder can be used in broiler chickens for up to 5.5% of the total diet, and such inclusion led to an improved feed conversion ratio and carcass growth. However, Van Ryssen *et al.* (2013) warmed against the inclusion of AP in broilers' diets This was evidenced by some trials in that such waste induced poor performance of the birds, although no symptoms of toxicity were observed at the end of the experiments.

Despite the positive effects referenced, avocado fruits have been associated with congestive heart failure related to severe cardiomyopathy in goats, sheep, horses, and ostriches (Stadler *et al.* 1991). Low doses develop aseptic mastitis in horses and goats, while high intake of the fruits of some avocado cultivars has poisoned budgerigars, birds, cats, mice, rats, horses, rabbits, cattle and goats, and canaries, among others, and possibly dogs (Kellerman *et al.* 2005). Persin has been cited as responsible for the toxicity of avocado peels and seeds, being considered a fungicidal toxin found in the leaves and fruits of the avocado tree. The lethal dose is characteristic of each animal species. The mechanism by which avocado compounds act is by triggering fluid accumulation in the lungs, leading to difficulty breathing, and death takes place due to oxygen deprivation. Fluid accumulation can also occur in the pancreas, heart, and abdomen (Buoro *et al.* 1994).

To use AP as livestock feed, the excessive amount of bioactive compounds in AP could be decreased by hydrothermal treatment. This was successfully applied to avocado seeds to reduce bioactive compounds and fiber contents to safe levels, and different boiling times were

investigated. Results showed a significant reduction in the fiber fractions and bioactive compounds as the boiling time increased when compared with the raw seeds, and iron was significantly higher in the treated samples than in the raw ones. Moreover, the energy values showed a slight increase from the raw at 30 min of hydrothermal treatment (Ibhaze 2017). Although persin was not analyzed in this work, this bioactive would probably follow the same trend as the other bioactive compounds.

The experimentation developed to feed PA to farm animals shows highly contradictory results. Probably, the toxicity or beneficial effects of PA in farm animals are due to the different levels of persin in the various PA, whose concentration is dependent on the type of avocado cultivar considered. Therefore, pending new research, it is advisable to use PA in mixtures with other by-products or, alternatively, to carry out hydrothermal treatments to reduce bioactive compounds included in PA to safe levels, according to the experimentation shown.

Conclusions

As exposed in this work, avocado waste, i.e., peels and seeds, contain suitable amounts of several health-enhancing compounds for farm animals. Avocado peels contain a great variety of phenolic acids and flavonol glycosides, while the seeds contain mainly flavanol monomers, procyanidins, and hydroxycinnamic acids. Other highly relevant phytochemicals found in avocado by-products are acetogenins, which have antimicrobial, antibacterial, and spore germination inhibiting effects, and whose occurrence is restricted to Annonaceae and Lauraceae. The utilization of avocado by-products to feed farm animals could become an important tool for adequate by-products management to ensure ecologically and sustainable production. Comprehensive experiments in farm animals are needed, including not only the use of pure phytochemicals but also feeding animals with raw by-products to ensure cheap exploitation and sustainability of the production processes. Also, rigorously toxicological experiments clarifying the possible toxic effects of avocado by-products cited in some farm animals are needed, while studies on nutritional aspects of avocado by-products such as the aminoacyl composition of the various seeds and peels varieties, will help to discern the nutritional potential of these by-products. Furthermore, the reduction of bioactive compounds contained in avocado by-products through different treatments, such as hydrothermal ones, should be enhanced. Not only in terms of the composition of the resulting product, but also in terms of the health of farm animals fed with such by-products.

Acknowledgements

The author acknowledge the financial support of Vicerrectorado de Investigación e Innovación of University of Almería (Project 2020/00001014), Junta de Andalucia (Proyect P20_00806), Campus de Excelencia Internacional Agroalimentario (ceiA3), and Centro de Investigación en Agrosistemas Intensivos Mediterráneos y biotecnología Agroalimentaria (CIAMBITAL).

Author Contributions

JLGG conducted the study, performed the literature search, the data extraction and wrote all parts of this paper.

Conflicts of Interest

The author declare no conflict of interest of any sort.

Data Availability

I hereby declare that the data relevant to this paper is available and will be provided on request.

Ethics Approval

This study does not involve human subjects. Thus, ethics approval is not required.

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