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Review

The Potential of Grape Polyphenols Additive in Pig Nutrition: Chemical Structure, Bioavailability and Their Effect on Intestinal Health of Pigs

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Abstract: The recognition of the necessity for employing natural additives in animal feed has grown alongside the ban on antibiotics in the animal feed sector. Grapes, as well as by-products of the wine-making industry (grape marc and seed extracts), possess biologically active chemical constituents that can be used to improve animal production by incorporating them into animal feed. Grapes are a valuable resource of polyphenols, especially flavonoids, stilbenes and phenolic acids, most of them showing therapeutic or health-promoting properties. The purpose of this review is to elucidate the impact of polyphenols on animal gut health. The first section of the review discusses the chemical structure of the major polyphenols in grapes and the polyphenols' bioavailability and metabolism in pigs. The second and major part of the review reviews the results of investigations into the antioxidant, antimicrobial and prebiotic effects of grape polyphenols in pig diets, as well as their regulation of intestinal barrier functions through signalling pathways and intestinal responses. All of this is supported by previous research, findings and conclusions. There are fewer recorded pig studies, but the inclusion of up to 9% grape by-products resulted in improved performance with an increased mean daily gain. Ultimately, this analysis concluded that supplementation of pigs with grape phenolic compounds as natural feed additives enhanced their antioxidant capacity, improved humoral and cellular immune responses, and promoted gut ecosystem biodiversity and the overall production performance in pigs.

Keywords: grape by-products; polyphenols; antioxidant; growth performance; pig

Citation: Proca, A.C.; Horodincu, L.; Solcan, C.; Solcan, G. The Potential of Grape Polyphenols Additive in Pig Nutrition: Chemical Structure, Bioavailability and Their Effect on Intestinal Health of Pigs. *Agriculture* **2024**, *14*, 1142. https://doi.org/10.3390/agriculture14071142

Academic Editor: Gang Shu

Received: 30 May 2024
Revised: 10 July 2024
Accepted: 12 July 2024
Published: 14 July 2024

1. Introduction

The continuous growth of the human population in recent decades has led to an increase in the global demand for animal products, one of which is pork [1]. In order to meet this demand, it is essential to improve the efficiency of pig production [2,3]. Feed accounts for the largest proportion of the total cost of livestock production [4]. Therefore, the identification of economically and sustainable viable alternatives to conventional feed is of paramount importance. Agro-industrial by-products are a notable option, as they are generated in large quantities annually, most of which are discarded or landfilled as waste [4].

Numerous studies have shown that the reuse of agricultural by-products can not only reduce costs but also improve environmental conditions [5,6]. These by-products are abundant and inexpensive and are abundant sources of nutritional constituents such as fibres, protein, minerals, antioxidants and vitamins. Due to their content of bioactive principles, they are well suited for use as supplementary ingredients in pig diets [7]. In addition, these co-products may be utilised as antibacterial agents, thus limiting the use of antibiotics [4]. A fundamental characteristic of phenolic compounds is their considerable antioxidant activity. In fact, certain phenolics can have multiple benefits, such as boosting immune function, reducing inflammation, promoting gut health and having antimicrobial activity.

The powerful antioxidant properties of procyanidins, a compound found in grapes, have been of great interest to scientists around the world. Scientific research has shown that the antioxidant capacity of procyanidins is about 20 times stronger than that of vitamin E and 50 times stronger than that of vitamin C [8]. Grapeseed procyanidins extracted from grapeseeds have been widely recognized as having potentially beneficial properties, including an antioxidant effect [9], an anti-inflammatory action [10,11] and an immunomodulating capacity [12]. Procyanidins' biological effects are well-studied in animal models and in vitro [13–15]. Their potential as feed additives or feed ingredients in animal farming, however, is still mostly unexplored.

The aim of this review is to elucidate the biological activity mechanisms of these bioactive compounds with the goal of discovering their potential applications and highlighting recent scientific advancements that support their useful properties, their bioavailability and their use as additives or ingredients in pigs' diets.

2. Grape Polyphenols: Their Chemical Structure and Bioavailability in the Gut

Grapes (*Vitis* spp.) are one of the most agronomically, zootechnically and economically important plant species due to their various uses in wine production and other food by-products [16]. The use of grapes has a long history, dating back to ancient times, spreading throughout the modern world, especially through the wine industry.

Grapes are one of the most cultivated fruit fruits in the world, with about 74 million of tones produced annually. Of this, 37.5% is cultivated in Europe, 36.5% in Asian countries and 17.2% in the USA [17]. Grapes grow on all continents in temperate regions characterised by abundant rainfall, hot, dry summers and mild winters [18]. About 50% of grape cultivation is used to produce wine; a third is consumed as raw fruit, and the remaining grapes are transformed into food items such as raisins, juice, grapeseed extract and oil and vinegar [17]. For this reason, there are numerous literature studies reviewing and characterising grapes, wine and grape derivatives such as grape pomace [19,20].

The production of *Vitis* spp. is of major importance due to the nutritional value and pharmaceutical properties of grapes, both raw and dried, as well as their derivatives, such as extracts and grapeseed oil [21,22]. Grapes are one of the richest fruits in carbohydrates (17 g/100 g), are high in calories (65 kcal/100 g) and have a relatively low glycemic index. Grape berries represent approximately 20 to 25 percent of the total mass of grapes used in the production of wine [23]. Grapes contain vitamin B6, thiamine and vitamin C and are an excellent source of manganese and potassium. They represent one of the most abundant sources of polyphenols, which are mainly found in the grape skin [24]. Grape berries contain fibres, protein, lipids and minerals. Essential amino acids such as lysine, arginine, glutamic acid, aspartic acid, glycine methionine and threonine are found in the protein of dry weight [25–27].

By-products derived from fruit are manufactured on a vast scale throughout the world, and the industrial grape segment is of great importance to the economy [4] and generates several thousand tonnes residues every year, creating a major waste management challenge [28]. These solid residues include a variety of by-products, such as vine shoots, stems, skins, seeds, lees, filter cakes and grape pomace. Until recently, grape marc was considered to be industrial waste and was left to decompose in the fields of the nearby winery or in huge landfill sites [29]. About 20% of the total weight of grapes used in winemaking is estimated to be marc. After the grapes have been processed for wine, they can be divided into two fractions: seedless grape marc (the remaining pulp, stalks and skins) and seeded grape marc (Figure 1). The first fraction is rich in fibres, while the seed is mainly used for its oil, containing unsaturated fatty acids. On a dry matter basis, the seeds account for 38–52% and the hulls for 5–10% of the grape pomace [30]. Grapeseeds are composed of fibres (47%, of which 60–70% is indigestible), complex carbohydrates (29%), fat (13%) rich in essential fatty acids, protein (11%), minerals and extractable phenolic compounds such as phenolic acids and flavonoids [23,31]. The protein from grape seeds contains all the essential amino acids, with an average of 3.6% methionine and 4.5% lysine. The main amino acids are those found in the grape, with the exception of threonine, which is present at 4.0% [32]. Grapeseed extract and grapeseed oil are two by-products obtained from grape seeds after processing wine or grape juice. The seeds are extracted, dried and purified to obtain these co-products, like grapeseed extract, which contains a high concentration of polyphenols, and grapeseed oil, high in essential fatty acids [13]. These substances are known for their powerful antioxidant action, preventing harmful oxidative reactions and removing free radicals from the body [33,34], as well as their antimicrobial properties [31].

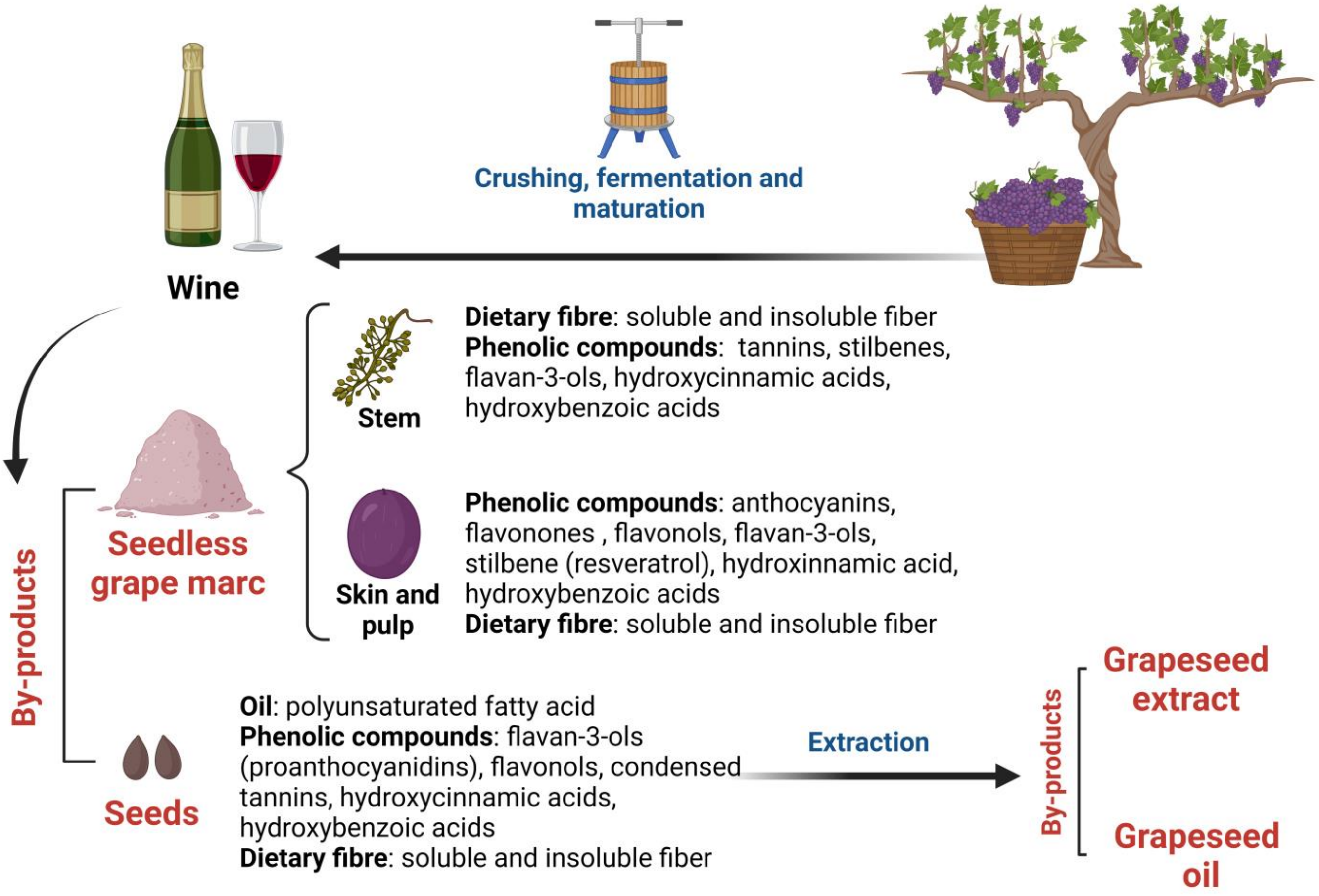


Figure 1. The process of obtaining grape by-products and the main components of each part. The figure was created with www.BioRender.com (accessed on 10 May 2024).

The nutrient values of grape by-products, such as fibre and organic matter digestibility and energy content and bioactivity, are the main determinants of their potential value in animal feed. Grape by-products are especially high in a variety of polyphenols. Previously called tannins, polyphenols have been seen as antinutritional agents because their occurrence in some legumes has negative impacts on the nutrition of animals. The main restrictions on the use of tescovine in monogastric diets are the presence of a lignified cell structure and the high tannin level. Grape skins and seeds contain the highest levels of dietary fibres (74% by weight), mainly hemicelluloses, covered with a whitish film [35] and tannins [36]. However, the stalk of the grape is lignified and consists entirely of tannins, which make up over half of the overall polysaccharides, making it an economical source of fibre [37].

In the last few years, in vivo and in vitro studies have demonstrated the positive effects of administering these bioactive substances. In fact, fibre enhances intestinal peristaltic action and works as a bacterial buffer and prebiotic, promoting the growth of friendly bacteria in the gut [4], while polyphenols may serve as an antioxidant, antimicrobial and immunomodulator [4,15,24,31,38–41]. Dietary fibre and polyphenolic substances can help to maintain or increase the growth performance and health of pigs according to the dosage and processing of the grape by-products included in the diet [15,38,39].

The chemistry of grape by-products is dependent on a number of factors, including ripeness, grape variety, soil type, weather conditions, geographical location [42,43] and the wine-making technology used [4,44,45]. All these aspects can alter the physical qualities of the grapes, including their flavour, aroma, texture and appearance [42]. Polyphenols are compounds with one or several phenolic hydroxyl groups linked to one or several benzene rings [46]. They are divided into classes based on the number of phenolic groups contained and the structural elements attached to these benzene rings [47]. The biosynthesis of these components in plants has been the subject of much research [48–50]. An understanding of the biosynthesis of phenolic components is essential for the effective management of their production in plants and, hence, of the by-products that can be used in pig feed.

Polyphenols are a group of chemicals biosynthesised in plants via the shikimate- or acetate-pathway of photosynthesis. These secondary metabolites are beneficial to the plant's lifespan and are formed as naturally occurring phytoalexins to confer pathogen resistance, protection against damage caused by the sun's ultraviolet rays and to deter predators due to their strong astringency when ingested [51,52]. Polyphenols are ubiquitous in plant life and are often part of our daily diet, occurring in a wide variety of fruits, some greens and even drinks [51,53,54]. The identification of phenolic compounds in grapes began in the late 19th century and continues today. To date, more than 8000 different phenolic structures have been discovered [51,55,56]. In general, polyphenols can be divided into about 10 classes with different basic structures, according to Bravo et al. [51]. Within grape pips, polyphenols can be divided into two major categories: flavonoids and non-flavonoids. Flavonoids in grape pips are divided into flavanols, flavonols, proanthocyanidins, anthocyanins and anthocyanidins, while non-flavonoids include phenolic acids and stilbenes [4,30,57] (Table 1).

Table 1. Chemical structures of major grape non-flavonoids.

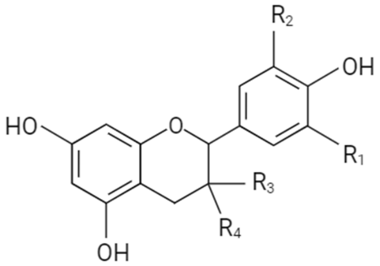
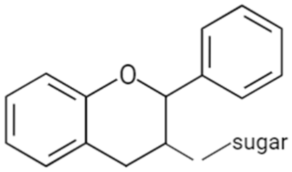
Typ	Name	Chemical Structure	Radicals				Compound
			R1	R2	R3	R4	
Flavonoid	Flavanol		H	OH	H	OH	Catechin
			H	OH	OH	H	Epicatechin
			H	OH	G	H	Epicatechingallate
			PH	OH	OH	H	Epigallocatechina
			OH	OH	H	OH	Gallocatechin
	Anthocyanin						

Table 1. *Cont.*

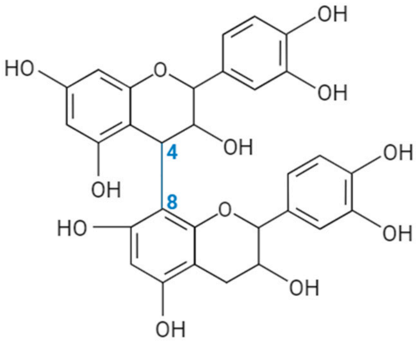
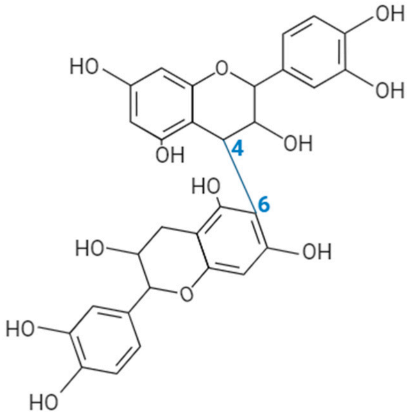
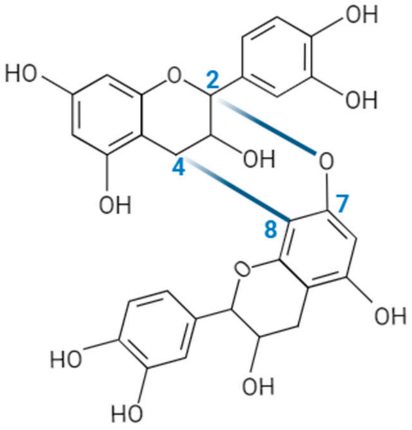
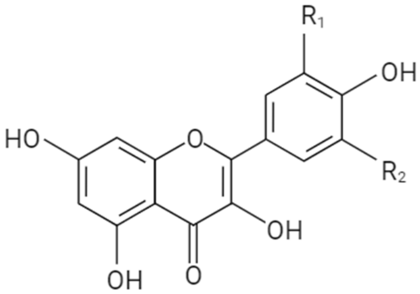
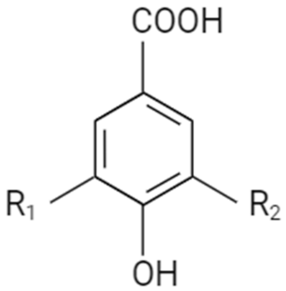
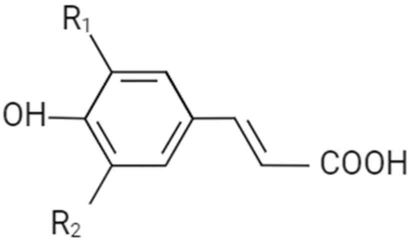
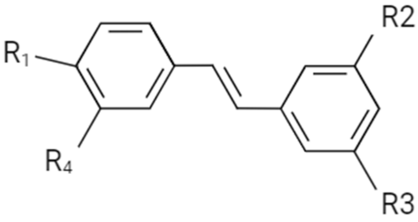
Typ	Name	Chemical Structure	Radicals		Compound
Flavonoid	Proanthocyanidin B-type link				
	Proanthocyanidin B-type link				
	Proanthocyanidin A-type link				
	Flavonol		R1	R2	
			OH	OH	Myricetin
			OH	H	Quercetin
			H	H	Kaempferol
			OCH3	H	Isorhamnetin

Table 1. *Cont.*

Typ	Name	Chemical Structure	Radicals				Compound
Non-flavonoid	Hydroxybenzoic acid		R1	R2			
			OH	OH			Gallic acid
			OH	H			Protocatechuic acid
			OCH3	OCH3			Syringic acid
			H	H			P-Hydroxybenzoic acid
	Hydroxycinnamic acid		R1	R2			
			OH	H			Cafeic acid
			OCH3	H			Ferulic acid
			OCH3	OCH3			Sinaptic acid
			H	H			p-Coumaric acid
	Stilbene		R1	R2	R3	R4	
			OH	OH	OH	H	Resveratrol
			OH	OH	OH	OH	Piceatannol

Flavonoids are biologically the most potent phytonutrients within the grape polyphenols. They can be divided into more than 13 subclasses with more than 6000 different chemical structures [58–60]. According to studies by Bravo et al. [51], Motohashi et al. [61] and Aron and Kennedy [62], the basic structure of flavonoids is two phenyl radicals (rings A and B) joined by three carbon atoms to create an oxygen-containing heterocycle (ring C). The flavonoids are further classified according to their oxidation state and distribution of hydroxyl radicals on the heterocyclic ring [47,63] (Table 1). The diversity of the chemical structures of flavonoids is responsible for their wide range of physiological and biological activities. The majority of the flavonoids are contained in the grape skin's epidermal cells, while around 60–70% of all of the polyphenols are found in the seeds [16,64,65]. Flavonoids are the major class of soluble phenolic compounds found in grapes and are the major contributors to the biological activity of grape products [66]. The bioactivities of flavonoids are significantly influenced by the degree of glycosylation, the type of sugar radical present and the subsequent acid esterification [67]. Therefore, selecting different varieties with distinct flavonoid profiles can have effects on pig health. Flavonoids are renowned for their cardioprotective, neuroprotective, antimicrobial, anti-ageing [68–72], antidiarrheal [73], antibiotic [74], anti-inflammatory [75,76] and antioxidant properties [55,77]. They also aid in improving vision [78] and cardio-protection [79], among other benefits [8]. Additionally, they provide UV protection, define flower colour, help attract pollinators and protect tissues from pathogen invasion or damage from oxidative stress [80].

The most common flavonoids in grapes are flavanols, including monomers, such as catechin and epicatechin, oligomeric proanthocyanidins (2 to 5 units) and polymeric polyphenols (more than five units), which are known as condensed tannins [81,82]. The structure of flavanols includes a hydroxy radical in the C3 atom and a B-ring linked to the C2 atom [63,83,84] (Table 1). Flavanols are synthesised before flowering, and their concentration increases until veraison—the time of grape ripening [85]. The main flavan-3-

ol monomers in grapes and wine include (+)-catechin, (−)-epicatechin, (−)-epicatechin-3-gallate [86] and (−)-epigallocatechin, and traces of (+)-gallocatechin. In the skins and stems of grapes, the main monomers are (+)-catechin, (−)-epicatechin and (−)-epicatechin 3-O-gallate, while the seeds contain catechin, epicatechin 3-O-gallate and epicatechin [87,88]. The contents of (−)-epicatechin and (+)-catechin are higher in red than in white varieties [89]. Catechin is the most abundant flavanol found in seeds and grape skins, with traces also in grape pulp [30]. These compounds contribute to the bitterness in wine and may cause some astringency. Initial studies on these compounds began in the 1920s [90] and were further explored in grape seeds and during wine production. A significant proportion of flavan 3-ol monomers originate from grape seeds [91–95], with higher temperatures, higher alcohol concentrations and longer extraction times increasing their concentration in wine. Flavanols are not glycosylated in food, unlike other flavonoid classes [30].

Proanthocyanidins (condensed tannins) are made up of two to five flavan-3-ol subunits. They are called oligomeric proanthocyanidins because the acid-catalysed cleavage of polymer chains produces anthocyanidins. Flavan-3-ols are characterised by the presence of the hydroxyl group (-OH) at position 3 of the flavonoid basic structure. The chemistry of tannins varies according to their origin, containing up to twenty hydroxyl radicals and a molecular mass of 500 Da to 3000 Da [96]. Structural variations between proanthocyanidins depend mainly on the interflavanic bonds, subclassified into type A (C2-O-C5 or C2-O-C7 bonds) and type B (C4-C6 or C4-C8 bonds) [62]. Procyanidin C1 is a C4-C8 bonded trimer [75,97,98] (Table 1).

The difference in interflavonoid bond positions and constituent units confers structural diversity to the higher oligomers, increasing the number of isomers with a polymerization degree [92,99–101]. Limited knowledge about proanthocyanidin chemistry is due to the analytical methods focusing on each oligomer as a class without identifying proanthocyanidins within each class [102]. Galloylated oligomeric proanthocyanidins are characteristic of condensed grapeseed polyphenols [103]. Tannins' ability to bind proteins underlies their protective characteristics [104] and nutritional benefits [105]. They have a distinctive odour and astringent taste and appear as a loose or shiny white or yellow powder [106,107]. Grapes and wine have one of the highest phenolic levels among fruits, vegetables and beverages. Depending on the variety, the proanthocyanidin content at the point of harvest can range from 0.5 to approximately 6.4 mg/g of fresh berry fruit weight [108]. Proanthocyanidins contribute to the astringency of red wines, extracted from the seeds, steams and skin [23]. About 30% of proanthocyanidins are in the seeds, and 15% are in the peel [109]. Extraction from seeds requires breaking the cell walls [110]. The final proanthocyanidin content in seeds is obtained at a later stage than in the peel, a couple of weeks after the onset of ripening. These components were among the most recent important phenolic compounds to be structurally identified [111,112]. Proanthocyanidins with a low molecular weight are found in very low concentrations and are easily hydrolysed [113], while higher molecular weight ones are associated with astringent and UV protective properties. These compounds are popular in functional food formulations for their health benefits [114–116]. The proanthocyanidin content is influenced by climatic and geographical conditions, grape variety, fertilisation, cultivation practices and soil [89].

Anthocyanins, with the aromatic B-ring attached to the C2 position, have two bonds in the heterocyclic ring. They constitute the glycosylated version of the anthocyanidins (aglycone), resulting from the linkage of the C3 hydroxyl group with the sugar moiety. Anthocyanins are the most prevalent polyphenols in the skins of red grapes and act as natural dyes [44,57,63,83,84,117]. They are mostly found in the skin, but in certain 'teinturier' (or coloured) varieties, anthocyanin pigments also accumulate in the berry pulp [118,119]. There is an intimate relationship between the levels of anthocyanin biosynthesis and the development of the berry, starting at 'veraison' when the biosynthesis of proanthocyanidins is complete and peaking at 'ripeness' [120]. There is a unique set of anthocyanins in each grape species and variety [121]. For instance, European grapes produce mainly 3-O-monoglucoside anthocyanidins, while muscadine grapes produce mainly 3,5-O-diglucoside anthocyanidins. The identification of the anthocyanin structure was preceded by scientific research into red wine's colour [122]. The general structure of anthocyanins was determined in the early 20th century [123,124]. The structures of the major anthocyanins in *Vitis vinifera* grapes were identified in 1959, with malvidin-3-O-glucoside as the main anthocyanin present, together with its acylated forms [125]. The work of Ribéreau-Gayon also demonstrated that anthocyanins in *Vitis vinifera* are structurally distinct from those found in other species, being exclusively monoglucosides, while the non-vinifera species also contain 3,5-diglucosides. Subsequent studies on the distribution and structure of anthocyanins in grape species have furthered our understanding of grape anthocyanins [126–128].

Found mainly as 3-O-glycosides in grape skins, flavonols are the next most abundant flavonoid in grapes. In wines and juices, they can also be found as aglycones, such as kaempferol, quercetin, isorhamnetin and myricetin, due to hydrolytic attack by acids in processing and during storage [129]. The flavonol structure includes a C2-C3 double linkage, where the hydroxyl radical is at the C3 atom and the B-ring is attached to the C2 atom of the keto group [130] (Table 1). The flavonol profile varies between grape varieties, but generally, quercetin 3-O-glucoronide and quercetin-3-O-glucuside predominate in most varieties [121]. Quercetin derivatives, isorhamnetin and kaempferol, are found in both white and red varieties, while the derivatives of myricetin are found only in red grapes [121,129].

Unlike flavonoids, non-flavonoid polyphenols have a single ring as their main structure. The non-flavonoid molecules found in grapes include stilbenes and phenolic acids [47,63,131]. Phenolic acids in grapes are derivatives of hydroxycinnamic acids, such as caffeic, p-coumaric, ferulic and sinapic acids, and hydroxybenzoic acids, such as gentisic, gallic, protocatechuic, p-hydroxybenzoic and syringic acids [16,47,63,131,132] (Table 1). These phenolic acids, especially hydroxycinnamic acids in the tartaric acid ester form, are the main phenolic components of white wine and are essential for its colour. They are mainly derived from grape pulp but are also found in similar quantities in red wines. In the mid-20th century, hydroxycinnamic acids were identified in grapes [125]. These compounds were earlier observed to be in the form of free acids. Later, it was discovered that grapes contain no free hydroxycinnamic acids but do have esterified tartaric acid [125]. Other compounds have been characterised [133,134] and shown in berries before ripening [93]. Stilbenes consist of two aromatic rings linked by an ethylene radical. The best-known stilbene is resveratrol. Stilbenes are found in grapes, wine and their derivatives [47,63,131] (Table 1).

Bioavailability is a measure of how much of a food's natural structure is available to its destination after it has been ingested through the gastrointestinal tract. The amount of a compound that is absorbed, metabolised and circulates throughout the body is called bioavailable [135]. Digestive metabolism, bioactivity, tissue partition, hepatic and intestinal metabolism, and absorption by intestinal epithelial cells are termed bioavailability [136]. Thus, bioavailability is rigorously based on bioavailability activities [137]. The bioavailability and efficient delivery of polyphenols to target tissues is required to explain the biological effects of polyphenols. It is, therefore, important to have an understanding of how they are absorbed, metabolised and excreted out of the body (Figure 2).

Absorption studies are complicated by the molecular complexity of polyphenol-rich extracts or foods due to factors such as the degree of conjugation and polymerization with other phenols. The majority of polyphenols are available in plants in the form of esters, polymers or glycosides, which cannot be absorbed in their original structure. Most polyphenols are linked to cell wall components like proteins, arabinoxylans or other organic compounds such as lipids and acids [138,139]. Before they can be absorbed, they must be hydrolysed by microbiota or endogenous enzymes. After absorption, polyphenols are recognised by the body as foreign substances, resulting in relatively low bioavailability compared to macro- and micronutrients.

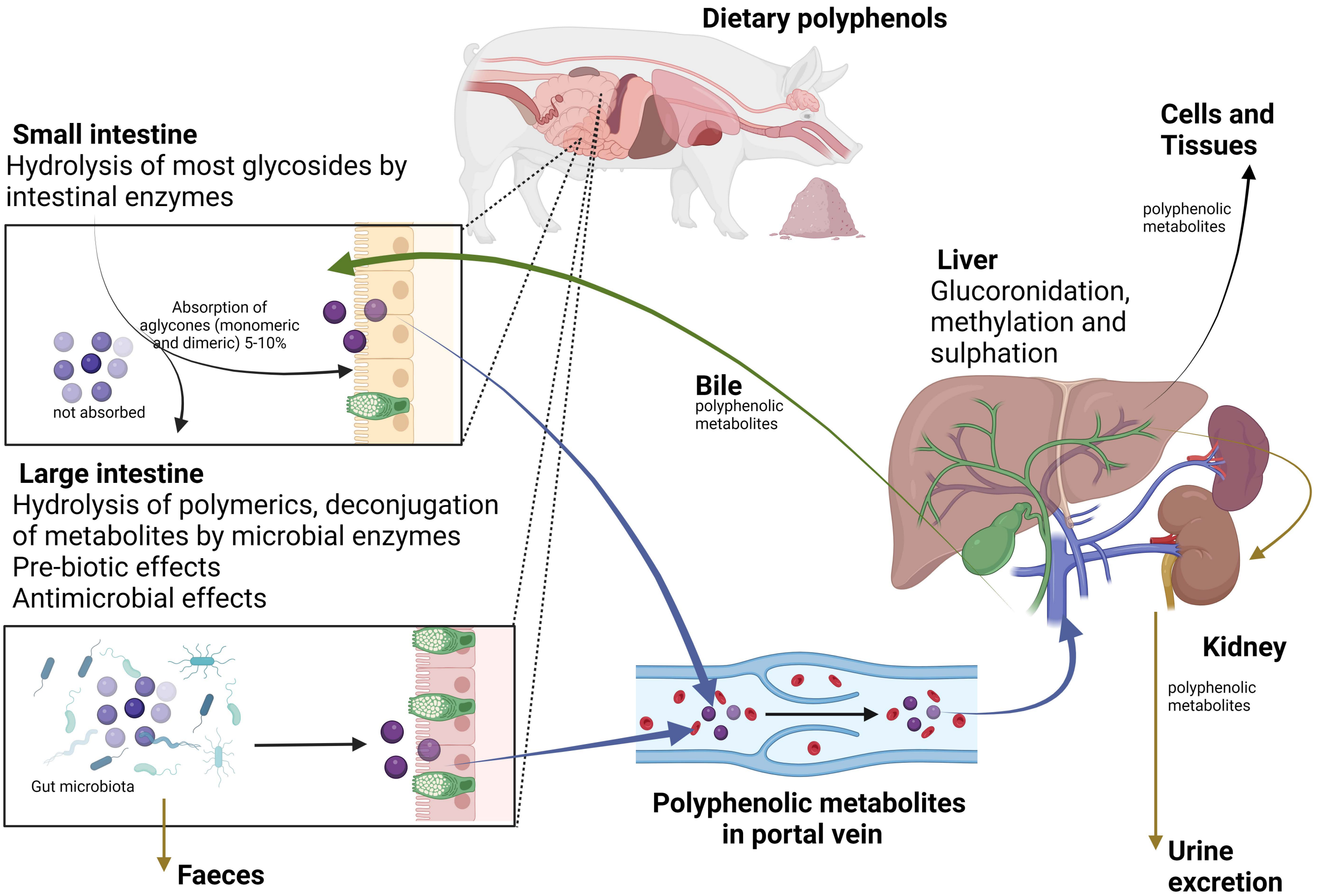


Figure 2. Bioavailability of polyphenols in the digestive tract of pigs. The figure was created with www.BioRender.com (accessed on 3 June 2024).

The metabolism of polyphenols involves a number of common reactions aimed at reducing their cytotoxic potential by increasing hydrophilicity and favouring biliary or urinary excretion [54]. It is the chemical structure of the polyphenols, rather than their concentrations, that defines the speed and magnitude of absorption, as well as the characteristics of the circulating metabolites in the plasma. According to estimates by Faria et al. [140,141] and Corrêa et al. [140,141], the absorption of polyphenols in plant substances in the small intestine is less than 5–10%.

Depending on their complexity and degree of polymerisation, the absorption of polyphenols may vary. Polyphenols with a simple structure (monomeric and dimeric) are easily absorbed in the small intestine, whereas oligomeric and polymeric polyphenols reach the colon almost unchanged [54,142–144]. Previous studies have shown that procyanidin trimers and dimers are very stable under gastric and duodenal digestion conditions, and the consumption of dimers is considered to be approximately 100 times lower than that of monomers [145]. Furthermore, it has been observed that proanthocyanidins from peels tend to have a greater degree of polymerisation than those obtained from seeds [146]. However, recent research suggests that only polymers with polymerisation degrees lower than 5 are absorbed [147] or are subsequently degraded to their flavan-3-ol monomers in the intestinal lumen.

After their absorption, less complex polyphenols, known as aglycones, can be hydrolysed and bio-transformed in enterocytes and then in hepatocytes [148,149]. A variety of water-soluble metabolites, such as methyl derivatives, glucuronides and sulphates, are formed during this process. These metabolites rapidly enter the circulation, are distributed to various tissues and are subsequently eliminated in the urine [54,150]. Some of these metabolites are excreted in the bile into the colon, where they are hydrolysed by bacterial enzymes, particularly beta-glucuronidase. This enterohepatic recycling may extend the duration of polyphenols in the organism. However, most polyphenols reach the colon in an intact state, where they preserve the intestinal barrier integrity and exert their bioactive properties, among them anti-inflammatory and antioxidant activities. While polyphenols are distributed to various tissues, the majority end up in the colon, where they are subject to the enzymatic activity of the gut microbiota along with metabolites eliminated in the lumen of the intestine. The result of these microbial activities is the production of a wide range of metabolites that can be incorporated into the blood stream or be excreted in the faeces. Metabolites taken up by the body are transported via the portal veins to the liver, where some can be glucuronidated, methylated or sulphated, and then dispersed to various tissues or eliminated in the urine.

The binding affinity of polyphenolic metabolites to albumin, a factor influenced by the chemical composition of the polyphenolic components, determines their bioavailability in target tissues [151]. Moreover, certain metabolites may exhibit prebiotic effects, promoting an increase in beneficial gut bacteria and inhibiting the growth of pathogenic strains [152–156]. Therefore, the microbiota of the gut has a pivotal function in both the degradation of polyphenols and the formation of metabolites responsible for the biological effects of polyphenols.

Bioavailable nutrients, as defined by Prada et al. [157], represent the most crucial fraction of nutrients reaching the bloodstream. The focus is on releasing these nutrients into systemic circulation rather than solely considering the total excreted amount. Moreover, many beneficial bioactive substances are often present in forms that are not readily available, emphasising the need to modify dietary matrices for enhanced accessibility. Variations in flavonoid bioavailability, including plasma and urinary concentrations and compound availability, may be due to many factors, including the source, chemical characteristics, food matrix, dosage, individual differences, analytical methodology and detection limits [158,159]. Research gaps exist in understanding the grape by-product polyphenols' digestibility in livestock and how it affects nutrient digestibility. Significant differences based on sex and species affect xenobiotic metabolism, leading to variations in polyphenol metabolite spectra, tissue distribution and blood concentrations [160–167].

3. Antioxidant and Anti-Inflammatory Effects of Grape Polyphenols in Pig Feed

Oxidants consist of both radical and non-radical molecules containing oxygen, chlorine or nitrogen and are called reactive oxygen species (ROS), chlorine or reactive nitrogen species (RNS). Oxidants can be produced in the course of metabolism (superoxide radicals formed in the mitochondrial chain of respiration) during a response to inflammation (superoxide radicals produced by the oxidase NADPH in the activated immune cells) and as a result of exogenous insults (free metals such as iron and copper, which lead to the production of OH radicals form H_2O_2) [168].

Animals can be exposed to oxidative stress due to a number of factors, including diets containing fungal toxins, elevated ambient temperatures, a number of pathological situations in which the immunological system is heightened (vaccinations, infections), ascites, pulmonary hypertension and coccidiosis [169–171].

The antioxidant system works to avoid oxidative stress through the reduction and/ or scavenging of oxidants and is made up of the following: (1) Antioxidant enzymes (catalase—CAT, glutathione peroxidase—GPX and superoxide dismutase—SOD); (2) antioxidants of low molecular weight (vitamin C, vitamin E, uric acid, carotenoids, glutathione and polyphenols); and (3) proteins sequestering free-transition metals (ferritin, metallothionein and ceruloplasmin) [168].

Phenolic compounds, which are natural metabolites, are recognised for their ability to counteract oxidative stress, which is associated with serious disorders of the metabolism by damaging the extracellular and cellular macromolecules [172,173]. These components are highly antioxidant and are essential in providing health benefits [174]. Flavonoids, a wide class of lower molecular weight compounds, have significant antioxidant activity.

Due to their particular chemical structure, they are able to decrease oxidative stress by various pathways [70,175]. In vitro, for example, flavonoids can serve as chain-breaking and protective antioxidants, scavenging alkoxyl, peroxyl, hydroxyl and superoxide radicals and blocking low-density lipoprotein oxidation. (LDL) [176,177]. Furthermore, flavonoids may function as metal chelators and blocking enzymes that are involved in ROS production, such as protein kinase C, xanthine oxidase, lipoxygenase, glutathione S-transferase, cyclooxygenase, mitochondrial NADH oxidase, mitochondrial succinoxidase and microsomal monooxygenase [173,177,178].

The antioxidant role of phenols depends on the position and number of hydroxyl groups and their relationship to carboxyl functional groups [173,179,180]. Among phenolic compounds, the monomer forms are not as efficient as hydrogen scavengers compared to phenols in the polymer form [181]. The structure–function relationship [182] and glycosylation [183] influence the antioxidant properties of phenolic compounds. In other words, the ability to donate hydrogen or electrons and delocalise unpaired electrons in the ring of the phenol is the primary mechanism to protect the molecules from oxidation [184,185]. ROS may damage the intestinal mucosal barrier and interfere with nutrient absorption, and antioxidants play a critical role in neutralising these radicals and maintaining an optimal environment at the intestinal surface [186].

Oxidants activate NF-κB, a key regulator of inflammation, and oxidative stress is closely linked to inflammation [187]. In its inactive state, NF-κB is bound to inhibitory proteins in the intracellular cytosol and is found in approximately all animal cell types. Following oxidative stimulation and factors, for example, bacterial stimuli, viruses, UV radiation and cytokines, the repressor proteins are removed from NF-κB, allowing the translocation of active NF-κB. This allows active NF-κB to relocate to the nucleus and enable the transcription of a wide range of inflammation genes [188]. The genes targeted by NF-κB encode typical proteins like adhesion molecules, inflammatory enzymes, chemokines, inflammatory cytokines and a variety of receptors [188–194]. Many of the proteins regulated by NF-κB, including chemokines and cytokines, promote the formation of oxidants from activated neutrophils and mitochondria, increasing oxidative stress and creating a ‘vicious circle’ [188,192,194–196]. If no intervention can be made to stop this vicious circle and the production of oxidants becomes overproduced, the process of inflammation will become chronic [188,192,197–201], and the cells and tissues of the body will be damaged, and in the case of pigs as farm animals, the following diseases can occur: lung inflammation, intestinal inflammation and septicemia [202].

By stimulating the production of immunoglobulins and decreasing the release of pro-inflammatory cytokines, polyphenols can improve gut health and immunity in the diet of monogastric animals [203]. These phenolic components may also enhance the action of antioxidant enzymes, thereby limiting inflammation [204]. Studies have shown that grape polyphenols may decrease inflammation by regulating inflammatory pathways and reducing levels of reactive oxygen species (ROS). Being natural substances, the flavonoids and proanthocyanidins in grapes may act in multiple ways against chronic inflammation, which may make them better than single-target synthetic chemical anti-inflammatory medications [205,206].

The anti-inflammatory activity of the polyphenols is achieved through complex cellular pathways. The majority of these mechanisms involve an inhibition of NF-κB, which is the key regulatory molecule in inflammation. Polyphenols can inhibit NF-κB activation through the inhibition of phosphorylation and proteasomal degradation of IκB, and this activity may be, at last, partly attributed to the polyphenols’ antioxidant properties [207]. Polyphenols can directly scavenge free oxygen radicals and cause transcription factor Nrf2 to be activated. This causes a number of antioxidant enzymes to be activated [208]. Both direct ROS scavenging and Nrf2 activation help prevent oxidative stress, which initiates the pro-inflammatory responses through the activation of NF-κB, mitogen-activated protein kinases (MAPK) and activator protein 1 (AP-1) [209]. Furthermore, polyphenols can engage transcription proteins such as peroxisome proliferator-activated receptor gamma (PPAR-γ), thereby counteracting inflammation through the inhibition of NF-κB activation [209].

The activation of Nrf2 by polyphenols is an example of a common hormonal pathway activated by polyphenols and other phytochemicals. The idea of hormesis suggests that while higher doses of some polyphenols may be harmful, sub-toxic levels consumed by herbivorous animals may cause minor cellular stress responses such as Nrf2 activity. This leads to the initiation of vitagenesis, including genes encoding antioxidants, biotransforming enzymes and heat shock proteins, which maintain cell stability under stress conditions and confer tolerance to greater stress [210]. Stress-related phytochemicals not only offer protection against increased doses of the same compound but against other less specific compounds or stress factors, such as metabolic, oxidative and inflammatory stresses [211], which are relevant to farm animals. In response to these non-specific stressors, such as ROS and reactive nitrogen species, Nrf2 cytoprotective pathway activation stimulates autophagy [212]. Autophagy is a well-conserved lysosomal 'self-digestion' process. This process leads to the breakdown of long-lasting proteins, as well as cell organelles and the generation of fatty and amino acids and nucleotides that may be reused for protein synthesis and ATP production in times of cellular stress [213]. Activation of autophagy by hormetic phytochemicals and caloric restriction reduces ER, inflammatory and oxidative stresses, thereby contributing to an increased cellular capacity and organismal health [213].

Grapeseed proanthocyanidins (PACs) were shown to have strong anti-inflammatory activity by scavenging radicals, preventing the peroxidation of lipids and inhibiting the production of pro-inflammatory cytokines [214]. In the in vitro studies, PACs showed anti-inflammatory activity on enteric cells and macrophages [215,216]. Reduced inflammatory cytokine production, oxygen free radicals (ROS) and NF-κB translocation were observed when the macrophages or dendritic cells were exposed to pro-inflammatory stimuli in the presence of PAC [114,217]. PACs also effectively attenuated inflammation-induced mitochondrial dysfunction and oxidative stress in epithelial cells. The precise mode of action of PACs is still not fully understood, but it appears that they modulate the signalling pathways related to lysosomal activity and secondary messengers [217,218]. These results are in agreement with the immunological modifications seen in vivo, suggesting that at least part of the anti-inflammatory effects of PAC are due to the direct modulation of immune cells in the mucosa [219–221]. In addition, PAC can activate innate immune cells, such as γδ-T cells [222,223], which have a key role in enhancing the immune response of the mucosa against pathogens and in signalling the activation of other immune cells, including neutrophils [224]. Stimulating intestinal organelles with CAP causes a marked increase in the regulated antimicrobial defence, suggesting that the gut of mammals has developed to perceive CAP as a sign to enhance the innate immune response to avoid and reduce inflammation [225].

The gastrointestinal luminal surface is protected by a mucus gel layer, providing an essential physicochemical barrier against chemical, enzymatic, mechanical and microbial damage. Mucin is a major glycoprotein of this layer. It forms an effective barrier that prevents microbial adhesion and subsequent invasion [226]. It is thought that polyphenols may influence the properties of this protective layer, as well as the absorption of nutrients and the viscoelastic environment of the bacteria in the gut [227]. Some research has suggested that certain polyphenols, such as resveratrol and ellagic acid, can increase the production of mucus by goblet cells in the intestinal lining, indicating a potential benefit in inflammatory bowel disease [228,229]. Polyphenols have also been found to interact with the gastrointestinal mucus layer, acting as crosslinkers for purified gastric and duodenal mucin, which could affect mucus layer elasticity [227].

Another important mucosal defence mechanism is the production of antimicrobial peptides. These are known as host defence peptides or antibiotic peptides. Due to their antimicrobial and immunomodulatory activities, these molecules play a crucial function in innate immunity. To date, more than 400 peptides with antimicrobial activity have been reported in animals and plants, which are produced by both immune cells and mucosal epithelia [230]. In pigs, information on the activity and function of defensins is limited. However, several types of defensins have been studied, including porcine β-defensin 1 (pBD-1) [231]. Recently, new potential variants of β-defensins have been described on the basis of sequence homology [232]. It is believed that these peptides, such as pBD-2, may play an essential role in promoting gut health. More recently, Wan et al. [233] have reported that the EGCG black tea extract decreased the translocation of bacteria in IPEC-J2 cell monolayers by inducing the production of the antimicrobial biallelic peptides, pBD-1 (porcine b-defensins 1) and pBD-2, having greater antimicrobial efficacy towards *E. coli*. A subsequent mechanical investigation showed that the EGCG extract from black tea increased pBD-2 but not pBD-1 through the p38 mitogen-activated protein kinase (MAPK)-dependent pathway. This research indicates the possibility that some polyphenols, such as EGCG, may modulate epithelial immune barrier function by inducing defensin production. Additional research is needed to gain a greater perspective on how polyphenols such as EGCG affect intestinal mucosal barrier function and to assess the potential of other polyphenols in this regard.

Few investigations have evaluated the impact of polyphenol-rich grape by-products on pro-inflammatory gene expression in the gut in relation to the possible influence of polyphenols on the inflammation of pigs. A nutrition study by Gessner et al. [234] found that a diet containing grapeseed extract and grape pomace meal reduced the expression of a variety of pro-inflammatory markers in the duodenum of pigs during growth. The grape pomace and seed extracts supplementation also resulted in an improvement in the ratio of villus height to crypt depth, indicating that plant-derived polyphenols may have a beneficial effect on gut microarchitecture. In a different study, two plant extracts rich in polyphenols were used, namely either an extract of grapeseed and grape pomace meal or an extract of hops, both at a dietary level of 10 g/kg of feed. In different areas of the gut (duodenum, ileum or colon), both extracts reduced the expression of several inflammatory genes (CCL2, IL-1B, ICAM-1, TNF, IL-8) [235] (Table 2.). In particular, the genes are controlled by nuclear factor κB (NF-κB), the key inflammatory regulator [190,236,237] (Figure 3). Chemokines and cytokines are a class of small proteins that are essential for the modulation of a wide range of biological events, such as adaptative and innate immunity and the regulation of inflammatory responses. They may be generated by a different cell type, for example, by immune cells (like lymphocytes, macrophages and dendritic cells) or other cell types (like intestinal epithelial cells (IECs)). Some cytokines are expressed constitutively by the intestinal epithelium to maintain the homeostasis and growth of epithelial cells; these include granulocyte-macrophage colony-stimulating factor (GM-CSF), tumour growth factor alpha (TGF)-a and interleukins IL-18, IL-15, IL-10, IL-6 and (IL)-1 [238]. However, when the gut becomes inflamed, there is a substantial upregulation of cytokines and chemokines, including IL-8, IL-6, IL-1b and TNF-a [239]. Excessive secretion of these pro-inflammatory cytokines may play a central role in the pathogenesis of inflammatory bowel diseases (IBD) such as ulcerative colitis and Crohn's disease. Properly controlling the secretion of these cytokines is critical to maintaining intestinal homeostasis [240]. Significant reductions in the inflammatory mediators Nrf2 and NF-κB in the mucosa of the duodenum were observed in pigs fed diets rich in polyphenols, including seed extracts and grapeseed extract, which reduced the risk of intestinal disease. The potent anti-inflammatory and antioxidant properties of polyphenols, by reducing the production of reactive oxygen species locally in the small intestine, may be responsible for this inhibition of Nrf2. In contrast, no effects on NF-κB and Nrf2 gene expression were observed in pig liver. In pig liver, however, no effects were observed for NF-κB and Nrf2 gene expression. For example, dietary supplementation with grapeseed procyanidins at doses of 100–150 mg/kg resulted in improved serum IgM and IgG concentrations, considered as indicators of the humoral immune responses, in a study by [15] in young piglets. According to research by Ramiro-Puig and colleagues (2007) [241], the action of polyphenols on the humoral defence response is based on their effect on B-cells and on their differentiation in the direction of immunoglobulin-secreting cells. In the same context, Hao and colleagues (2015) [15] found that grapeseed teskovine-supplemented diets enhanced serum levels of IL-2, a key cytokine in the differentiation of T- and B-cells. The use of the grapeseed cake diet in the above experiment resulted in a statistically significant increase in IgA levels in plasma following 24 days of grapeseed polyphenol supplementation in the Taranu 2018 diet [242]. After the consumption of curcumin-derived polyphenolic compounds, a comparable elevation in intestinal IgA concentration has been observed in rats [243]. Secretory immunoglobulin A is the major form of immunoglobulin in the lumen of the intestine and has multiple properties essential for mucosal immunity and homeostasis. The secretory component of sIgA confers protection against degradation by resisting digestive and proteolytic enzymes found in the intestinal tract [244]. sIgA is localised in the intestinal lumen, an environment rich in microbes, unlike other types of antibodies, such as IgG, which are found in an almost sterile systemic compartment. As a result, the function of sIgA is different from other antibodies, exerting its effect through steric inhibition, receptor blocking or immune elimination, resulting in a lower inflammatory response [245].

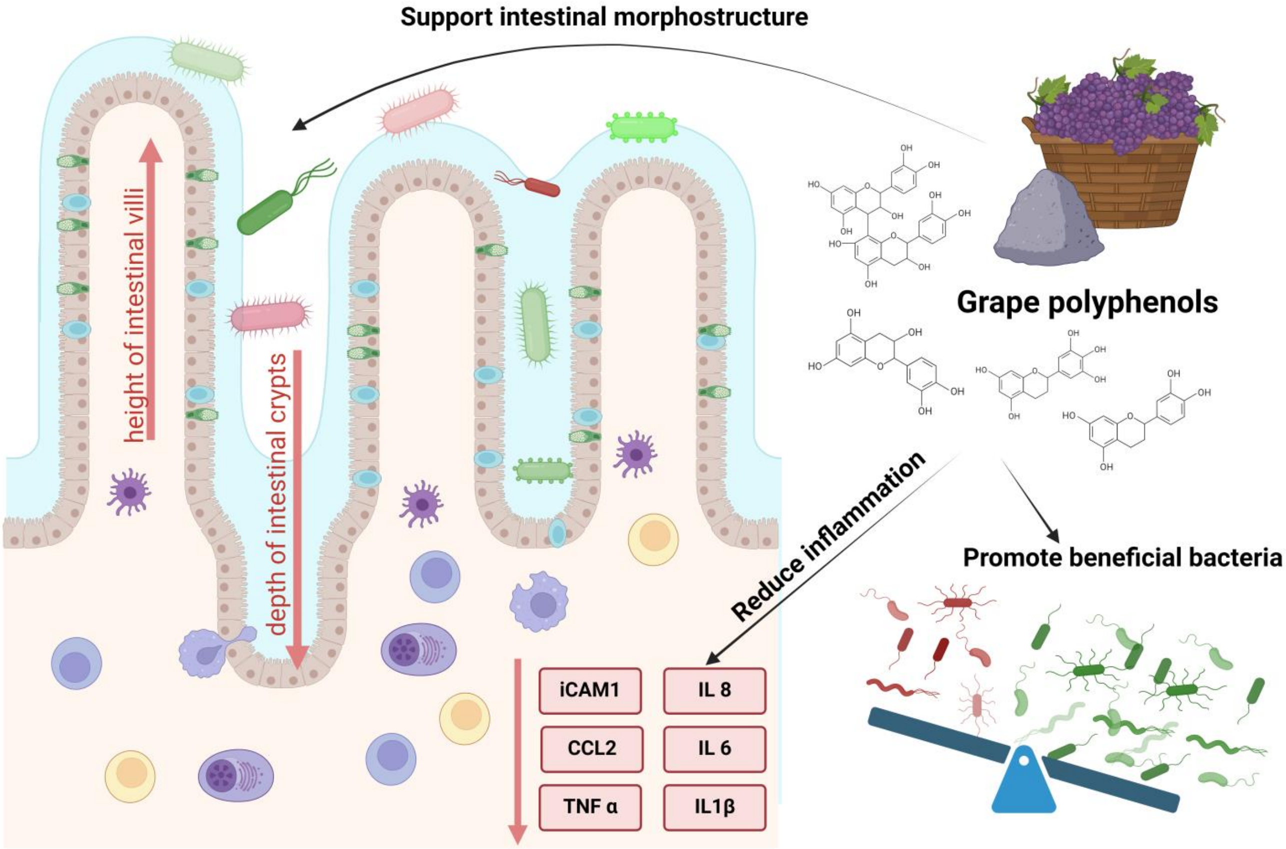


Figure 3. Effect of polyphenols on intestinal health. The figure was created with www.BioRender.com (accessed on 27 May 2024).

In pigs, adding a mixture of vegetable extracts, including grape seeds (2%), to the diet reduced plasmatic TBARS production in the weaned piglets without affecting the total antioxidant capacity, according to research by Zhang et al. [246] involving the modulation of plasma antioxidants. In another study by Gessner et al. [234], grapeseed and grape tescovine did not affect the plasma and liver TBARS concentrations in piglets or plasma antioxidant defences. Furthermore, the TBARS-MDA levels and liver antioxidant capacity in pigs on the high grapeseed inclusion diet were not significantly different from those in the control diet in a report by Taranu et al. [242]. Based on several studies to date, Gessner et al. [247] found that polyphenols from plants had a lesser impact on antioxidant capacity in healthy subjects, partly due to their lower bioavailability. However, due to their systemic anti-inflammatory effects, these compounds may improve the overall antioxidant balance and reduce free radical formation in challenged animals.

Table 2. Major physiological effects of grape by-product polyphenols in pigs.

Grape By-Product	Dose	Effect	References
Fermented grape pomace	3%	ADFI, final bodyweight and ADG were not affected. FCR decreased	[248]
Grapeseed cake	5%	ADG and ADFI were not affected Elevated plasma IgA levels and TBARS were significantly reduced	[242]
Complex polyphenpol extracts, including grape seeds	1%	Reduced the level of plasma MDA	[246]
Grapeseed extract (procyanidins)	0.04%	ADG increased and FCR decreased Increased expression of CAT, SOD and GSH-Px genes associated with antioxidant activity in the liver and could reduce MDA levels in muscle tissue, liver and serum	[39]
Grape pomace	5%	Higher jejunal villus height and villus height/crypt depth ratio ADG, ADFI and FCR were not affected	[39]
Grapeseed extract (procyanidins)	250 mg/kg	Improving the barrier function and morphology of the intestinal mucosa Enhanced the biodiversity of the gut ecosystem	[249]
Grapeseed and grape marc extract	1%	Increased small intestine villus height/crypt depth ratio Gain/feed ratio improved Duodenal mucosal inflammation inhibition	[234]
Grape pomace	9%	Increased ADG and final body weight Enhancement of antioxidant mechanisms and prevention of oxidative stress damage to lipids and proteins Enhances intestinal barrier function and health	[250]
Resveratrol	0,2%	Antimicrobial effect: *E. coli* and *Salmonella* Bacteria growth promoting activity: *Lactobacillus* spp.	[251]
Grapeseed extract	1%	Reducing *E. coli*-induced diarrhoea in weaned pigs	[252]
Grape seeds	8%	There has been an increase in *Bacteroidetes* phylum and a significant decrease in *Firmicutes* phylum	[253]
Grapeseed extract	1%	Microbiome ecological shift	[254]
Grapeseed procyanidins	0.5, 1, and 1.5%	No significant effect on growth performance, increased antioxidant capacity, improved humoral and cellular immune responses, reduced incidence of diarrhoea	[15]
Grape seeds and grape marc	1%	Modifies intestinal microbiota and reduces inflammation	[235]

4. The Antimicrobial and Prebiotic Effects of Grape Polyphenols in the Intestine of Pigs

An important tool for improving growth performance and feed efficiency is the manipulation of gut function and microbial habitat in livestock with feed additives. Research into alternative options for increasing the antimicrobial efficacy in animal production has become a priority due to the increasing antimicrobial resistance of pathogens isolated from humans and animals and the ban on the use of antibiotics as feed additives [255].

The concept of a "healthy gut" has gained popularity in recent years, as gut dysfunction has been associated with a variety of diseases, both at the local and systemic levels [256]. A disturbance in the immune homeostasis of the gastrointestinal tract (GIT) results in a weakened intestinal barrier, increasing susceptibility to infection with opportunistic pathogens and facilitating the translocation of intestinal bacteria to the basal part of the mucosa, which can lead to systemic inflammation [257,258]. It is well established that the modulation of gut microbiota benefits gut function. This includes improvements to the integrity of the gut barrier, a reduction in bacterial components entering the circulation and stimulation of the immune system to adapt [259]. In line with this, modulation of gut microbiota by plant polyphenols has been reported to be associated with reduced levels of systemic inflammatory markers, such as C-reactive protein, as well as reduced tissue inflammatory gene expression [152,154,156].

There is an increasing body of evidence that indicates the potential importance of gut microbiota as an underlying factor in the observed benefits of polyphenols on health [260]. The intestinal microbiota has been demonstrated to metabolise dietary polyphenols into bioactive compounds with diverse physiological significance. Furthermore, it has been shown to influence the gut bacterial population's composition and activity [261]. It can be observed that dietary phenolic compounds are frequently modified by gut microbiota and that gut microbial populations are influenced by dietary polyphenols in a bidirectional phenol–microbiota interaction. It is evident that polyphenols and their metabolites exert a profound influence on gut ecology. This is because a considerable proportion of these compounds are not fully absorbed, but are metabolised in the liver, excreted in the bile as glucuronides and accumulate in the ileum and colonic lumen [262]. The presence of significant quantities of unabsorbed phenols in feed can have a substantial impact on the gut environment, exerting a regulatory influence on the growth of specific components of gut microbiota.

The precise mechanism by which polyphenol-rich foods affect the composition of the gut microbiota remains unclear. This is an active area of research. A considerable field of study has been devoted to the metabolism of PAC molecules by the gut microbiota, with a particular focus on the colon [263]. It has been demonstrated, at least in vitro, that the bacterial metabolism of PAC is influenced by the degree of polymerisation (DP). It has been demonstrated that polymers are more resistant to degradation in comparison to catechin monomers [264]. The stimulation of gut microbiota-mediated polyphenol anthocyanin digestion in the in vitro models resulted in the active depolymerisation of polyphenols, followed by the appearance of phenolic metabolites. These metabolites exhibited similarities to those observed in the in vivo systemic circulation of animals fed with polyphenols [264]. It can be concluded that polyphenols may act as a direct prebiotic substrate in a manner similar to dietary fibres. Furthermore, the direct antibacterial effects of polyphenols have been extensively investigated. It is established that PAC induces the growth inhibition of certain bacteria, either by inhibiting enzymes, depriving them of growth substrates or exerting a direct effect on bacteria cell membranes [265]. The in vitro studies indicate that polyphenols have the potential to interact directly with host intestinal cells, thereby stimulating the production of mucins and other proteins that may serve as a selective nutrient source for bacteria such as *Akkermansia* [225]. *Akkermansia muciniphila* abundance has been observed to increase significantly in several species, including mice, pigs and humans, in response to diets rich in prebiotics and probiotics [266–268]. This bacterium has been identified as a potential biomarker for gut health, given its association with mucosal barrier integrity and mucin production. Furthermore, *Akkermansia* is capable of producing metabolites that directly suppress inflammatory responses in the intestinal epithelium. This suggests that its enhanced response to certain dietary components may contribute to its purported health benefits [269]. Other metabolites with documented anti-inflammatory properties, such as short-chain fatty acids (particularly propionate), have also been observed to be elevated in the digesta of animals fed diets rich in polyphenols [267,270]. It is evident that bacterial growth may be indirectly influenced by the effects of PAC on host cells. It is evident that the consumption of PAC alters the composition of the gut microbiota and produces soluble metabolites with anti-inflammatory or immunomodulatory activity. This prebiotic capacity of PAC may be an important mechanism for the observed health benefits in various disease models.

The term "prebiotics" has been defined as non-viable dietary components that confer health benefits on the host by modifying the microbiota [271]. Polyphenols have the potential to fill the definition described above due to their capacity to combat pathogens. In contrast, beneficial bacteria remain unharmed or are even stimulated by polyphenols. In their study, Han et al. [249] demonstrated that GSP increased the abundance and diversity of bacteria in both the ileum and colon. This indicates that GSP has a considerable positive impact on the biodiversity of the gut ecosystem. The principal mechanism by which phenolic compounds exert their effect is their lipophilic nature, which permits their accumulation in the lipid layer of the bacterial membrane and mitochondria. This can have an impact on the normal function of these membranes and cellular organelles [272]. Furthermore, phenolic compounds have the capacity to enhance the permeability of the inner bacterial membrane, thereby reducing ATP production and inhibiting DNA gyrase. These processes are essential for the production of DNA and RNA in bacteria. Phenols can disrupt cellular homeostasis and induce bacterial cell death by denaturing proteins, which results in ion loss [273,274]. Another noteworthy aspect is the active role of phenolic compounds in combating microorganisms, which is attributed to their structural characteristics. The hydroxyl (-OH) groups present in phenolic compounds exhibit bactericidal activities, which facilitate the killing of bacteria and the inhibition of their growth [275].

The gut microbiota is frequently conceptualised as a 'metabolic organ' with the capacity to influence nutrient absorption and interact with the immune system [276–278]. A healthy microbiota composition can act as a physical barrier against infection. Conversely, a perturbed microbiota balance can increase susceptibility to pathogens, contributing to the development of a range of diseases, including obesity, inflammatory bowel disease and cancer [279–282]. Consequently, an understanding of the interactions between polyphenols and the gut microbiota is crucial for elucidating their impact on gut health. It is important to note that the bioavailability and bioactivity of polyphenols are significantly influenced by bacterial metabolism. Polyphenols can also influence the composition of gut bacteria, with one of the most studied aspects being their ability to inhibit the growth of certain bacteria. The antimicrobial activity of foods rich in polyphenols has been the subject of extensive investigation, with studies ranging from simple in vitro experiments to complex in vivo studies. For instance, in vitro studies have demonstrated that certain pathogenic bacteria, including *Escherichia coli*, *Staphylococcus aureus*, and *Candida albicans*, are susceptible to phenolic acids [283].

It can be demonstrated that the inhibitory effect of polyphenolic compounds on bacteria can be attributed to a number of complex mechanisms, the most significant of which are their ability to adhere to the cell membranes of bacteria, interact with the enzymes of bacteria and bind to the metal ions present in the environment [68,265,284,285]. For example, the extract of grapeseed, derived from the 'Bangalore Blue Grapes' variety of *Vitis vinifera*, was found to possess potent antibacterial activity against Gram-positive bacteria [286]. A series of experiments conducted with extracts of juice, skin and seeds from 'Ribier' black table grapes indicated that they possess significant inhibitory effects against the proliferation of *Listeria monocytogenes* [287]. A number of studies have demonstrated that red grape pigments, including anthocyanin pigments, grape juice and grape skin extract, display pH-dependent anti-Listeria activity, whereas the seed extract exhibits pH-independent anti-Listeria activity [287]. Extracts derived from red and white grape berries, seeds, pomace and stems also demonstrated significant antimicrobial activity against *L. monocytogenes*. Catechin, epicatechin and epicatechin gallate were identified as the major active compounds [288]. A substantial body of in vitro research [119,289–292] has demonstrated that flavonoids present in grape by-products possess the capacity to inhibit the growth of a range of organisms, including *Staphylococcus aureus*, *Escherichia coli*, *Candida albicans* and *Campylobacter* spp. Additionally, certain polyphenolic compounds, including resveratrol, hydroxytyrosol, quercetin and phenolic acids, have been demonstrated to possess antimicrobial activity against intestinal pathogens such as *Salmonella* spp. and *Helicobacter pylori* [293,294]. In addition, grape polyphenols have been demonstrated to inhibit the growth of a range of pathogens, with polymeric flavonoids (procyanidins) exhibiting greater efficacy than their monomeric counterparts [74].

The existing literature on the interaction of polyphenolic compounds with the gut microbiota in pig nutrition is limited. Nevertheless, the in vivo studies have demonstrated that resveratrol has the potential to serve as an alternative to antibiotics in counteracting the adverse effects of weaning stress on growth performance, immunity and the microbial environment in piglets exposed to *E. coli* and *Salmonella* spp. challenges [251]. The addition of grapeseed extract (GSE) (10 g/kg) to the diet of weaned pigs also resulted in a reduction in Escherichia coli-induced diarrhoea, as reported in reference [252].

A study by Fiesel et al. [235] observed that the consumption of grapeseed and grapeseed meal extract resulted in alterations in the microbial composition, which led to a reduction in the number of *Streptococcus* spp. and *Clostridium* spp. bacteria present in the faecal microbiota. Nevertheless, no differences in the number of microorganisms in the faeces and caecum were observed in weaned pigs fed polyphenol-containing extracts (including GSE), according to a separate study by Zhang et al. [295]. Furthermore, administration of grapeseed proanthocyanidins in pigs has been found to reduce *Campylobacter jejuni* infection. The mechanisms underlying the effects of grapeseed proanthocyanidins in pigs appear to involve improvements in the mucosal barrier function, which may result from reduced oxidative damage and, thus, less disruption to the epithelial tight junctions [250]. Grapeseed extracts have demonstrated the capacity to regulate the composition of the intestinal microbiota. In both in vivo [24,296] and in vitro studies, they have been shown to inhibit the growth of *Clostridium* spp. species. However, in a recent study [253], it was demonstrated that grapeseed administration resulted in a significant decrease in bacteria, such as *Lactobacillus*, *Lachnospiraceae*, *Bacteroidales* and *Campylobacter*, while having a positive effect on other species, such as *Megasphaera*, *Clostridiales*, *Anaerovibrio* and *Prevotella*. The higher relative abundance of *Megasphaera*, *Prevotella* and bacteria of the order *Clostridiales* observed in pigs fed the high grapeseed diet may have beneficial effects on the host due to their involvement in carbohydrate metabolism and synthesis of short-chain fatty acids [297]. *Prevotella*, *Megasphaera* and *Anaerovibrio* are strictly anaerobic bacteria that have been identified as the dominant species in the large intestine of pigs and are also abundant in the ileum [298–300]. These bacteria have been identified as playing a pivotal role in the breakdown of complex carbohydrates in the lower gastrointestinal tract [301]. It is possible that the growth of these bacteria in the colon of piglets fed a grapeseed-rich diet is a response to the increased fibre content of this diet.

The in vivo studies utilising grape borage have demonstrated an increase in the abundance of *Clostridiales*, which is consistent with the aforementioned results. An ecological change in the microbiome was observed in sows fed a diet containing grapeseed extract (1%) [254], characterised by an increase in *Lachnospiraceae*, *Clostridiales*, *Lactobacillus* and *Ruminococcacceae*. The effects of tea polyphenols were also observed in pigs and calves. There was a significant increase in *Lactobacilli*, a decrease in the total number of bacteria and *Bacteroidaceae*, and a downward trend in the number of *Clostridium perfringens* [302,303]. The class *Firmicutes* includes the order *Clostridia*, which comprises obligate anaerobic bacteria such as *Clostridium* [300]. The effects of *Clostridia* on animal health are diverse, and they constitute a normal component of the intestinal flora. It has been demonstrated that certain members of the *Clostridiales* family, such as *Clostridium difficile*, are linked to the onset of adverse effects such as inflammatory bowel disease [304]. Others, such as *C. leptum* and *C. coccoides*, are significant components of the gut microbiome and contribute to healthy ageing [305]. The *Ruminococcaceae* are typically associated with an enhanced feed conversion in piglets as a consequence of their capacity to degrade cellulose [306]. This process contributes to the conversion of complex polysaccharides, otherwise resistant to digestive enzymes, into more readily metabolizable forms of energy [307].

Given the beneficial roles of phenolic compounds, it can be posited that they may serve as effective natural feed additives. Furthermore, agricultural by-products represent an excellent source of phenolic compounds and antioxidants that can be employed as functional ingredients in animal feed [308]. The hypothesis put forth is that the positive effects on antioxidant status and a reduction in ROS levels observed in some porcine studies [309–311] cannot be attributed to the direct antioxidant effects of the diet. It is possible that these effects are secondary to improved gut health, thereby reducing the translocation of pro-inflammatory and prooxidative stimuli. Nevertheless, further studies are required to provide more evidence of the potential beneficial effects of plant polyphenols in pigs. The beneficial roles of phenolic substances can be exploited as effective natural feed additives (Figure 3). Furthermore, agricultural by-products represent an excellent source of phenolic compounds and antioxidants, which can be employed as functional feed ingredients [308].

5. The Effects of Grape Polyphenols on the Production of Pigs

The incorporation of polyphenols into the diets of farm animals has the potential to enhance production performance and the oxidative stability of their feeds [312]. The literature on the influence of grape by-products on animal growth performance is inconclusive, with studies reporting either enhanced growth, depressed growth or no effect [248]. This apparent inconsistency appears to depend on the amount of polyphenols in grape products, which may interact with the digestive enzymes and gut proteins to affect nutrient digestibility and, thus, animal performance [248].

In growing pigs, the performance of the animals, as indicated by the body weight and gain/feed ratio, was enhanced by the administration of grapeseed and grape tannin meal containing 8.5% polyphenols at a dosage of 1%. This improvement was not due to an enhanced digestibility of nutrients but rather to alterations in the composition of the microbial population and the downregulation of several pro-inflammatory genes in different regions of the gut [234,235]. Similarly, another study [248] conducted over 15 weeks in pigs demonstrated that a diet supplemented with 30 g/kg of fermented grape seeds improved their nutrient digestibility without affecting their growth. Similar outcomes were observed by Taranu et al. [242], who noted that pigs fed 5% grapeseed cake exhibited no change in performance. Consequently, the total polyphenol content of the diet was probably insufficient to affect nutrient digestibility and, as a consequence, animal performance.

It is notable that the incorporation of grapeseed cake into the diet of GS pigs led to a notable reduction in plasma cholesterol levels. This finding is consistent with the previous observations from animal and human studies that have identified similar beneficial effects of grape by-products or whole grapes [313,314]. Polyphenols, including catechin, gallic acid, epicatechin and other active compounds in grape seeds, have been linked to reduced cholesterol absorption by inhibiting pancreatic enzyme cholesterol esterase, resulting in reduced cholesterol solubility in the mycelia and thus blood [315–317]. Furthermore, it has been demonstrated that certain polyphenols, including resveratrol and epigallocatechin, are capable of binding directly to miRNAs, namely miR-33a and miR-122, which are key regulators of the genes involved in hepatic lipid metabolism. This binding may result in reduced cholesterol concentrations [318]. Furthermore, another study reported that diets containing a mixture of plant extracts, including grapeseed, had no effect on the blood parameters in piglets. It has been demonstrated that a dietary intake of antioxidants can influence the humoral immune response [295]. However, the effect may vary depending on the source, the ratio and the duration of administration [15,241,319].

In the field of animal production, oxidative stress has the potential to exert considerable influence. For example, it can result in a reduction in body weight due to the disruption of optimal metabolic processes. Additionally, oxidative stress can impact meat quality by increasing plasma corticosterone accumulation, which is associated with a reduction in the pigmentation of breast meat in broilers [320]. Additionally, it can cause biological damage to the DNA, proteins and lipids, which can result in adverse health effects that may impact the productive capacity of farm animals [321]. The replacement of 50% of the vitamin E in the diet with polyphenols had no effect on the growth performance. However, it may improve the antioxidant status of sows or their offspring [322]. In piglets, the addition of polyphenols, a mixture of apples, grape seeds, green tea leaves and olive leaves, to the diet has been shown to reduce plasma MDA levels [246]. A recent study [38] demonstrated that diets supplemented with grapeseed procyanidins, a type of phenolic compound, exhibited enhanced resilience to weaning stress. This was evidenced by an increase in the expression of antioxidant-related genes, including GSH-Px, SOD and CAT, in the liver. The levels of malondialdehyde (MDA) in the serum, liver and muscle tissue were found to be reduced [38]. The bioactive compounds were also responsible for an increase in the ratio of intestinal villus height to crypt depth when grape pomace was administered to piglets at 5% [39], 1% GSGME [250] and grapeseed proanthocyanidins at 250 mg/kg [249]. These data suggest that polyphenols may improve intestinal mucosal barrier function, which may explain the increase in average daily gain (ADG) and decrease in the feed conversion ratio (FCR) [38] and the improved effects on growth performance in piglets fed grape by-products [15]. The impact of grape by-products on pig growth performance depends mainly on the age of the animal and the dosage of the by-products. In principle, the effect of low levels of grape by-products on growth performance was reduced, but this was dependent on the animal's age and the doses applied. Despite the variability of the results between studies, the increase in ADG demonstrated by Kafantaris [250] (9% grape pomace) deserves to be highlighted as a promising effect for pig production.

6. Conclusions

Grape by-products have many industrial applications, which include animal feed. They are a valuable feed due to their richness in polyphenols, which can modulate intestinal microbiota and morphology and boost anti-inflammatory and antioxidant capacities, thus maintaining intestinal health and production in pigs. It is difficult to establish the ideal dose of polyphenols in animal diets due to the variable composition of the phenolic components in these by-products. The best results, both in terms of health and high pig production, were obtained when 9% grape marc was added to the diet. For pig diets, future studies could focus on the optimisation of the dose and digestibility of grape by-products.

Author Contributions: Conceptualization, A.C.P., L.H., G.S. and C.S.; methodology, A.C.P., L.H., G.S. and C.S.; validation, G.S. and C.S.; formal analysis, A.C.P., L.H., G.S. and C.S.; investigation, A.C.P., L.H., G.S. and C.S.; writing—original draft preparation, A.C.P., L.H., G.S. and C.S.; writing—review and editing, C.S. and G.S; supervision, C.S and G.S.; project administration, C.S.; funding acquisition, C.S. and G.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest.

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