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(71) Applicant: **EVOLVA SA** [CH/CH]; Duggingerstrasse 23, 4153 Reinach (CH).

(72) Inventors: **ELGAARD, Troels**; Skibsbyggervej 21, 2660 Brøndby Strand (DK). **SIMON, Ernesto**; Binningerstrasse 15, 1442 Münchenstein (CH).

(74) Agent: **AERA A/S**; Gammel Kongevej 60, 18th floor, DK-1850 Frederiksberg C (DK).

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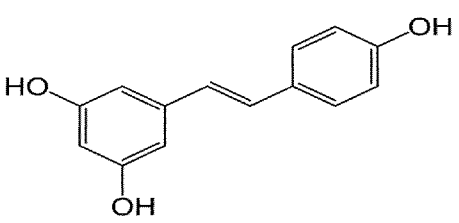


Figure 1. Chemical structure of trans-resveratrol.

(57) Abstract: Compositions comprising and methods of administering high-purity saponins and resveratrol for inclusion in the feed, feed additives or drinking water of warm-blooded animals and birds to improve health, reduce the need for antibiotics, reduce the nitrogen content of feces and increase the productivity and quality of farmed warm-blooded animals and birds.

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Title: Nature-identical supplements to improve the productivity of animals

Field of the Invention

[0001] The present invention relates to feeds, feed additives or drinking water supplements comprising a blend of high-purity nature-derived additives suitable for consumption by farmed animals and birds to increase the productivity of farmed animals and birds.

Background of the invention

[0002] Resveratrol and its derivatives are phytoalexin stilbenes found in very low concentrations in grapes, peanuts, cranberries, blueberries, strawberries, *Polygonum cuspidatum* and some other botanical sources. The content of resveratrol and resveratrol glycosides increases in grapes increases upon infection with *Botrytis cinerea* (Roldan 2003; Sahin et al. 2010; Alagawany et al. 2015).

[0003] In reared animals, resveratrol has been shown to reduce the oxidative stress in heat-stressed broilers and to improve the weight gain (Liu et al. 2014), and to help ameliorate the negative effects of aflatoxins present in broiler feeds (Sridhar et al. 2015). Aflatoxins enter feeds as a result of infestations of *Aspergillus flavus* and *parasiticus*, which are abundant in warm and humid regions and may contaminate crops in the field, at harvest, during transportation or storage. It is known that aflatoxins ingested in feed carry through to meat or dairy products and are passed up the food chain, including products for human consumption.

[0004] Furthermore, resveratrol has natural antibacterial properties, which can be used in both food preservation and medicinal use (Paulo et al. 2010), and may also be a potent antiviral molecule against DNA and RNA viruses (Campagna & Rivas 2010). Resveratrol in diets for quail has shown to increase the serum vitamin E level (Sahin et al. 2010).

[0005] Resveratrol is an antioxidant, and its use as a feed additive has also shown to reduce the levels of oxidative stress markers in meat and to improve pork meat quality by increasing the longissimus dorsi pH_{24} (a measurement of pH increase in the longissimus dorsi muscle over the 24 hours following slaughter), shear force, drip loss, glycolytic potential, backfat depth, lactase dehydrogenase activity and mRNA level (Zhang et al. 2015).

[0006] Trials with newly weaned piglets have shown that the inclusion of 0.2% of a resveratrol containing product in the piglets' feeds improved the efficiency of the feed conversion and the daily live weight gain compared to the negative control group (Ahmed et al. 2013).

[0007] However, although there is much interest in the use of resveratrol in addressing a variety of health issues, difficulties associated with producing the compound restrict its use in feed, feed additives or drinking water supplements suitable for consumption by farmed animals and birds. In the current market, the most common resveratrol production processes relies on extracting resveratrol from Japanese knotweed, a plant from the polygonaceae family grown commercially in China. Unfortunately, the extraction process is labour intensive and the yield of resveratrol is low, which is especially a problem for large volumes of feed or additives required for commercial farming practices. Outside of Japan, where natural controls have co-evolved in the ecosystem, knotweed is considered a highly invasive non-native species. It is a rhizomatous herbaceous perennial, meaning that although the surface vegetation dies back every year, the plant spreads through an underground root system that can stretch up to 8 meters from the shoot. Since thorough excavation of all root fragments is almost impossible, the only practical means of control are repeated cycles of burning and/or chemical treatment. Thus large scale farming of Japanese knotweed does not permit sustainable crop rotation practices and poses significant risk to adjacent residential, recreational, and agricultural land. A further problem with conventional resveratrol extraction processes from farmed knotweed is the presence of contaminants. For example, commercially available resveratrol compositions are often contaminated with emodin, a natural product of the knotweed plant, which can induce diarrhoea if consumed. Diarrhoea is especially a problem in mammals in the days post weaning when the animals are generally dehydrated as a consequence of their reluctant transition from milk to water. However, diarrhoea is in general a very serious problem in farmed animals, to the extent that many farmers administer antibiotics prophylactically to ensure good animal health and improved overall production through consistently higher aggregate weight gain of the group.

[0008] Other contaminants that may be found in resveratrol derived from knotweed are ground and/or air pollutants from the environment in which the knotweed plants have grown. For example, very high concentrations of poly-aromatic hydrocarbons have been detected in commercially available resveratrol samples derived from knotweed plants grown in various locations in China. Table 1 shows the results of analysis using gas chromatography coupled to mass spectrometry performed on 40 g samples of commercially available resveratrol derived from knotweed plants grown in China (samples 1, 2 and 3) when compared with fermentation derived resveratrol (samples 4 and 5).

Contaminant	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5
Anthracene	14 µg/kg	15 µg/kg	250 µg/kg	<0.5 µg/kg	0.66 µg/kg

Benzo(a) anthracene	0.89 µg/kg	0.91 µg/kg	300 µg/kg	<0.5 µg/kg	<0.5 µg/kg
Benzo(a) pyrene	0.50 µg/kg	0.52 µg/kg	350 µg/kg	<0.5 µg/kg	<0.5 µg/kg
Benzo(b) fluoranthene	0.74 µg/kg	0.73 µg/kg	350 µg/kg	<0.5 µg/kg	<0.5 µg/kg
Benzo(ghi) perylene	0.52 µg/kg	<0.5 µg/kg	260 µg/kg	<0.5 µg/kg	<0.5 µg/kg
Benzo(k) fluoranthene	<0.5 µg/kg	<0.5 µg/kg	130 µg/kg	<0.5 µg/kg	<0.5 µg/kg
Chrysene	1.2 µg/kg	1.3 µg/kg	360 µg/kg	<0.5 µg/kg	<0.5 µg/kg
Dibenzo(a,h) anthracene	<0.5 µg/kg	<0.5 µg/kg	31 µg/kg	<0.5 µg/kg	<0.5 µg/kg
Fluoranthene	15 µg/kg	15 µg/kg	940 µg/kg	<0.5 µg/kg	<0.5 µg/kg
Fluorene	94 µg/kg	98 µg/kg	280 µg/kg	<0.5 µg/kg	1.3 µg/kg
Indeno(1,2,3-cd)pyrene	<0.5 µg/kg	<0.5 µg/kg	190 µg/kg	<0.5 µg/kg	<0.5 µg/kg
Phenanthrene	67 µg/kg	69 µg/kg	860 µg/kg	1.5 µg/kg	2.8 µg/kg
Pyrene	13 µg/kg	13 µg/kg	920 µg/kg	<0.5 µg/kg	<0.5 µg/kg
Sum PAHs (4 or less rings)	3.3 µg/kg	3.5 µg/kg	1 400 µg/kg	<0.5 µg/kg	<0.5 µg/kg
Sum of heavy" PAHs (5 or more rings)	1.8 µg/kg	1.3 µg/kg	1 300 µg/kg	<0.5 µg/kg	<0.5 µg/kg
Sum of all positive identified PAHs	210 µg/kg	210 µg/kg	5 200 µg/kg	1.5 µg/kg	4.8 µg/kg

Table 1: Polycyclic aromatic hydrocarbon content in resveratrol samples derived from knotweed grown in China (samples 1, 2 and 3) and in resveratrol derived from recombinant microbial fermentation (samples 4 and 5).

[0009] Polycyclic aromatic hydrocarbons (PAHs), otherwise known as polynuclear aromatic hydrocarbons, are chemicals released from incomplete combustion of organic matter, typically by the burning of fossil fuels in smelting, manufacturing, power stations, vehicles and home fires, as well as burning the by-products of agriculture such as crop residues (such as surface remains of Japanese knotweed itself) and dung. PAHs generally have low solubility in water, and are predominantly seen in solid form as particulate air pollution, soil or sediment pollution. Although cancer is the primary health risk of exposure to PAHs, they have also been linked to cardiovascular disease and poor fetal development. Hence, the administration to animals and birds of resveratrol extracts comprising environmental pollutants such as has been observed in knotweed-derived resveratrol may be undesirable not only for the animals and birds themselves, but raises concerns from the ultimate human consumers of the resulting farmed products (such as meat or eggs).

[0010] The rising global human population is placing increasing stress on the current means of production of food and on the sustainable use of land areas. There is an environmental need to maximize the efficient use of land already allocated to farming, whilst simultaneously reducing the impact of such modern farming practices to the surrounding natural and residential environments.

[0011] Therefore, in light of the current challenges to the domestic and commercial rearing of animals and birds, there is a growing need for effective, sustainable, environmentally friendly compositions and methodologies to benefit the health of farmed animals and birds, and to improve the quality and yield of farmed products resulting from farmed animals and birds.

Summary of the Invention

[0012] Provided herein are effective natural compositions and methods of their use in the rearing of animals and birds.

[0013] In some aspects, the combination of a stilbene or a methylated or glycosylated derivative thereof (such as resveratrol or pinosylvin) and saponins disclosed herein including but not limited to steroid saponins (as found for example in *Yucca schidigera,* or Fenugreek or *Trigonella foenum graecum*) and triterpene saponins (as found for example in Quillaia, *Quillaja saponaria*, tea seed, *Camellia oleifera*, Camellia tea, *Camellia sinensis,* liquorice, *Glychyrriza*

glabra or Quinoa) are shown herein to have very positive effects on animal performance when consumed by farmed animals or birds, including improving the weight gain, the feed conversion ratio, the efficiency of protein usage in feed, and/or the reduction of nitrogen in a waste stream In one such aspect the feces resulting from the farmed animals or birds has a reduced nitrogen content, making treatment of manure/effluent/sewage less problematic, and reducing the effects of surface run-off into the local ecosystem. In another aspect the air within and emanating from the animal or bird farming area has a reduced concentration of volatile nitrogen-containing molecules (such as ammonia), reducing unpleasant smells for the local human population and reducing the stress of the farmed animals or birds.

[0014] In one aspect, the combination of a stilbene or a methylated or glycosylated derivative thereof (such as resveratrol or pinosylvin) and saponins disclosed herein may be added to the feed or water of animals and birds to increase the weight gain. As evidenced herein, the resveratrol and saponins blend provides gain-improving effects.

[0015] In another aspect, the combination of a stilbene or a methylated or glycosylated derivative thereof (such as resveratrol or pinosylvin) and saponins disclosed herein may be added to the feed or water of farmed animals and birds to improve the feed conversion ratio.

[0016] In another aspect, the combination of a stilbene or a methylated or glycosylated derivative thereof (such as resveratrol or pinosylvin) and saponins disclosed herein is present in the feed or drink of farmed animals or birds to improve the protein usage from within the feed. In one aspect the combination of a stilbene (such as resveratrol or pinosylvin) and saponins disclosed herein is present in the feed or drink of farmed animals or birds as a partial replacement for protein in the food, i.e. permits the same weight gain from a feed with lower protein content than would normally be required to achieve that weight gain.

[0017] In another aspect, the combination of a stilbene or a methylated or glycosylated derivative thereof (such as resveratrol or pinosylvin) and saponins disclosed herein is present in the feed or drink of farmed animals or birds to decrease the nitrogen content of feces.

[0018] In some embodiments, the composition further comprises at least one additional active ingredient that is a natural antioxidant or attractant.

[0019] In some embodiments the combination of a stilbene or a methylated or glycosylated derivative thereof (such as resveratrol or pinosylvin) and saponins disclosed herein is applied to the feed or drink of farmed animals or birds in the final stage of their growth cycle (such as “finishers”) to increase the efficiency of the feed conversion (i.e. a low feed conversion ratio and/or high average daily gain).

[0020] In some embodiments the combination of a stilbene or a methylated or glycosylated derivative thereof (such as resveratrol or pinosylvin) and saponins disclosed herein is applied to the feed or drink of farmed animals or birds in the early stage of their growth cycle (such as

piglets, chicks, freshly weened young) to increase the efficiency of the feed conversion (i.e. a low feed conversion ratio and/or high average daily gain).

[0021] In some embodiments the combination of a stilbene or a methylated or glycosylated derivative thereof (such as resveratrol or pinosylvin) and saponins disclosed herein is applied to the feed or drink of farmed animals or birds in the stage of their growth cycle when they have the largest increase in biomass (such as "grower-pigs") to increase the efficiency of the feed conversion (i.e. a low feed conversion ratio and/or high average daily gain).

[0022] In some embodiments the combination of a stilbene or a methylated or glycosylated derivative thereof (such as resveratrol or pinosylvin) and saponins disclosed herein is applied to the feed or drink of farmed animals or birds during every stage of their growth cycle to increase the efficiency of the feed conversion (i.e. a low feed conversion ratio and/or high average daily gain). In the case of mammals, this may be from weaning to slaughter. In the case of birds, this may be from hatching to slaughter.

[0023] In some embodiments the combination of a stilbene or a methylated or glycosylated derivative thereof (such as resveratrol or pinosylvin) and saponins disclosed herein is applied to the feed or drink of farmed animals or birds to improve the quality of meat from the slaughtered farmed animals or birds.

[0024] In some embodiments the combination of a stilbene or a methylated or glycosylated derivative thereof (such as resveratrol or pinosylvin) and saponins disclosed herein is applied to the feed or drink of farmed animals or birds during lactation to improve the quantity and/or quality of milk from lactating mother animals (wherein a higher quality of milk is measured by higher fat and/or protein content of the milk).

[0025] In some embodiments the combination of a stilbene or a methylated or glycosylated derivative thereof (such as resveratrol or pinosylvin) and saponins disclosed herein is applied to the feed or drink of farmed female animals or birds to improve their fertility rates (as measured by higher rates of pregnancy and/or higher rates of successful completion of term).

Description of drawings and figures

Figure 1 provides the chemical structure of the stilbene trans-resveratrol.

Figure 2 provides the chemical structure of the saponin solanine.

Figure 3 provides the layout of the building where the pigs were housed in Example 1.

Detailed Description of the Invention

[0026] All publications, patents and patent applications cited herein are hereby expressly incorporated by reference in their entirety for all purposes.

Definitions

[0027] The articles "a" and "an" are used herein to refer to one or to more than one (i.e. to one or at least one) of the grammatical object of the article. By way of example, "an element" may mean one element or more than one element.

[0028] The term “comprise” and “include” as used throughout the specification and the accompanying claims as well as variations such as "comprises", "comprising", "includes" and "including" are to be interpreted inclusively. These words are intended to convey the possible inclusion of other elements or integers not specifically recited, where the context allows. For the purposes of describing and defining the present invention it is noted that the term “substantially” is utilized herein to represent the inherent degree of uncertainty that can be attributed to any quantitative comparison, value, measurement, or other representation. The term “substantially” is also utilized herein to represent the degree by which a quantitative representation can vary from a stated reference without resulting in a change in the basic function of the subject matter at issue.

[0029] As used herein, the term “about” refers to ±10% of any particular value.

[0030] As used herein, the terms “or” and “and/or” are utilized to describe multiple components in combination or exclusive of one another. For example, “x, y, and/or z” can refer to “x” alone, “y” alone, “z” alone, “x, y, and z,” “(x and y) or z,” “x or (y and z),” or “x or y or z.”

[0031] It is noted that terms like “preferably,” “commonly,” and “typically” are not utilized herein to limit the scope of the claimed invention or to imply that certain features are critical, essential, or even important to the structure or function of the claimed invention. Rather, these terms are merely intended to highlight alternative or additional features that can or cannot be utilized in a particular embodiment of the present invention.

[0032] The term “isolating" or “separating” means any human intervention which change the relative amount of the compound compared to another selected constituent in a given matrix to

a higher relative amount of the compound relative to the other constituent. In an embodiment, the compound may be isolated into a pure or substantially pure form. In this context, a substantially pure compound means that the compound preparation contains less than 10%, such as less than 8%, such as less than 6%, such as less than 5%, such as less than 4%, such as less than 3%, such as less than 2%, such as less than 1 %, such as less than 0.5% by weight of other selected constituents. In an embodiment, an isolated compound is at least 50% pure, such as at least 60% pure, such as at least 80% pure, such as at least 90% pure, such as at least 91% pure, such as at least 92% pure, such as at least 93% pure, such as at least 94% pure, such as at least 95% pure, such as at least 96% pure, such as at least 97% pure, such as at least 98% pure, such as at least 99% pure, such as at least 99.5% pure, such as 100 % pure by dry weight.

[0033] The term “synthetic” or “non-naturally occurring” means that a compound is not normally found in nature or natural biological systems. In this context, the term “found in nature or in natural biological systems” does not include the finding of a compound in nature resulting from releasing the compound to nature by deliberate or accidental human intervention. Synthetic compounds may include compounds completely or partially synthetized by human intervention and/or compounds prepared by human modification of a natural compound.

[0034] As used herein, “animals or birds” comprises farmed animals and birds, companion animals and birds, livestock, domesticated animals and birds, animals and birds bred for competition (such as racing), collection, working (such as hunting, draft, load bearing, human transportation), breeding or display. Animals include without limitation mono-gastric animals, pseudoruminants, ruminants, mammals, marsupials, and macropods (including wallabies and kangaroos).

[0035] As used herein, the term “ruminants” includes but is not limited to sheep, deer, antelope, goats, giraffes, yaks, buffalo, and cattle (including but not limited to cows). As used herein, the term “pseudoruminants” includes but is not limited to camels, alpacas, llamas, guanacos, and vicuñas.

[0036] As used herein, the term “mono-gastric animals” includes but is not limited to pigs, horses, sheep, rabbits, dogs, and cats.

[0037] As used herein, the term “birds” includes but is not limited to a chickens (such as a broiler, breeder or a laying hens), turkey, goose, duck, pheasant, quail, grouse, ostrich, emu or pigeon. As used herein, the term “broiler chicken” may refer to a chicken grown and slaughtered for meat, rather than a “laying chicken”, which may refer to a hen chicken grown for the production of eggs.

[0038] As used herein, the term “finisher pig” may refer to commercially reared pigs with a live weight of about 75 kg or higher, typically achieved as the pigs approach the final 4 weeks prior to slaughter.

[0039] As used herein, the term “piglets” may refer to commercially reared pigs from the time they begin eating solid feed in the farrowing house until they achieve 30kg, typically at the age of about 10-11 weeks old.

[0040] As used herein, the term “grower-pigs” may refer to commercially reared pigs in the growth stage when they increase mass from about 30kg up to about 75kg.

[0041] As used herein, the term “active ingredient” refers to a chemical compound or mixture of chemical compounds capable of treatment of microbial infections. As such, the active ingredient may have properties including but not limited to antimicrobial, antibacterial, and/or antiviral properties against microbes capable of infecting, growing or reproducing on or in the bodies of animals and birds. For example, the active ingredients may be effective against Gram positive and/or Gram negative bacteria.

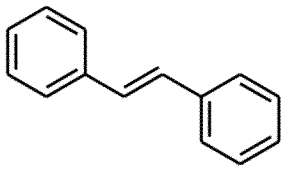
[0042] As used herein, the term “feed conversion ratio” (FCR) otherwise known as the feed conversion rate, refers to the ratio of the efficiency with which the animals or birds convert mass of feed into mass of desired output. As used herein in relation to animals and birds raised for meat (such as pigs, beef cows, fish and broiler chickens), the output is meat as measured by improvement in the final mass of the animal or bird. As used herein in relation to diary animals and lactating mothers, the output is milk. In some aspects lactating females (including but not limited to cows and sows) receiving compositions described herein comprising resveratrol and saponins may produce a greater volume of milk and/or a greater quality of milk (as measured by elevated protein and/or fat content, or lower cell count). As used herein in relation to layer birds (such as layer chickens, quail, ducks or geese), the output is mass of eggs. A higher FCR may be used to raise production rates of a farmed animal or bird, or it may be used economically to permit the provision of less feed by weight to the animal or bird whilst retaining or substantially retaining the same average increase in mass.

[0043] As used herein, the term “average daily gain” (ADG) refers to the average net increase in weight per animal or bird. As used herein in relation to animals and birds raised for meat (such as pigs, beef cows, fish and broiler chickens), the ADG is a measure of how rapidly the animals or birds are growing in mass, which may translate to a higher final live weight prior to slaughter, and/or to an earlier achievement of slaughter weight.

Compounds

[0044] According to some aspects, the stilbene or a methylated or glycosylated derivative thereof may be resveratrol (trans-resveratrol) or pinosylvin. Resveratrol may be provided at suitable concentrations as purified extracts of Japanese knotweed, yucca, grapes, etc, provided the extracts have undergone sufficient purification protocols such that they do not contain emodin nor polycyclic aromatic hydrocarbons. According to preferred aspects, the resveratrol for inclusion in the feed, feed additives or water may be produced by recombinant microbial fermentation, including but not limited to fermentation extract, purified resveratrol, or dried fermentation cake from recombinant microbes capable of producing resveratrol. Resveratrol derived from fermentation of recombinant microbes is preferred not least because it is inherently free of emodin and hazardous levels of Polycyclic Aromatic Hydrocarbons (PAHs).

[0045] As used herein, the terms "stilbene" and "stilbenoid" are interchangeable and refer to compounds based on the compound of formula (I):



(I),

wherein formula (I) may be substituted at one or more suitable positions. Exemplary substituents include, but are not limited to, halogen, cyano, nitro, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, hydroxy, C_1-C_6 alkoxy, thiol, C_1-C_6 alkylthio, amino, C_1-C_6 alkyl amino, di- C_1-C_6 alkyl amino, carboxyl, C_1-C_6 alkoxycarbonyl, amido, methyl, and glycosyl. Generally, stilbenes, including resveratrol, and flavonoids are produced in plants and yeast through the phenylpropanoid pathway as illustrated by the reactions shown in Figure 1.

[0046] As used herein, the term "phenylpropanoid" refers to compounds based on a 3-phenylprop-2-enoate backbone. Examples of such compounds include, but are not limited to, cinnamic acid, coumaric acid, caffeic acid, ferulic acid, 5-hydroxyferulic acid, sinapinic acid, cinnamoyl-CoA, p-coumaroyl-CoA, and the like.

[0047] As used herein, the term "phenylpropanoid derivative" refers to any compound derived from, synthesized from, or biosynthesized from a phenylpropanoid; *i.e.* a phenylpropanoid derivative includes any compound for which a phenylpropanoid compound is a precursor or intermediate. Examples of phenylpropanoid derivatives include, but are not limited to, stilbenoid compounds and chalcone compounds. Specific examples of phenylpropanoid derivatives include, but are not limited to, resveratrol, pinosylvin, pinocembrin chalcone, and pinocembrin.

[0048] As used herein, the term “dihydrophenylpropanoid” refers to compounds based on a phenylpropanoate backbone. Examples of such compounds include, but are not limited to, dihydrocinnamic acid, phloretic acid, 3,4-dihydroxyhydrocinnamic acid, hydroferulic acid, dihydrocoumaroyl-CoA, dihydrocinnamoyl-CoA, and the like.

[0049] As used herein, the term “dihydrophenylpropanoid derivative” refers to any compound derived from, synthesized from, or biosynthesized from a dihydrophenylpropanoid; *i.e.* a dihydrophenylpropanoid derivative includes any compound for which a dihydrophenylpropanoid compound is a precursor or intermediate. Examples of dihydrophenylpropanoid derivatives include, but are not limited to, dihydrostilbenoid compounds and dihydrochalcone compounds. Specific examples of dihydrophenylpropanoid derivatives include, but are not limited to, phloretin, phlorizin, dihydropinosylvin, dihydropinosylvincarboxylate, 3-O-methyldihydropinosylvincarboxylate, 4-isoprenyl-3-O-methyldihydropinosylvincarboxylate (amorfrutin 1), 3-O-methyldihydropinosylvin, 4-isoprenyl-3-O-methyldihydropinosylvin (amorfrutin 2), 5-hydroxy-lunularic acid, and dihydroresveratrol.

[0050] As used herein, the terms “phenylpropanoid pathway,” “phenylpropanoid derivative pathway,” “phenylpropanoid derivative synthesis pathway,” and “phenylpropanoid derivative biosynthesis pathway” are interchangeable and refer to any biosynthesis pathway in which a phenylpropanoid is a precursor or intermediate.

[0051] The term “stilbene” or a derivative thereof can be hydroxylated derivatives of stilbene and are thus encompassed by the term “stilbene” as used herein. The term “stilbene” includes but is not limited to at least one of resveratrol, dihydroresveratrol, and pinosilvin; a glycosylated stilbene comprising piceid (3-resveratrol monoglucoside or 5-resverarol monoglucoside), resveratroloside (4'-resveratrol monoglucoside), Mulberroside E (3,4'-resveratrol diglucoside), 3,5- resveratrol diglucoside, and 3,5,4'-resveratrol triglucoside and their dihydro- reduced equivalents; a methylated stilbene comprising pterostilbene (3,5-dimethoxy-4'-hydroxy-trans-stilbene), 3,5,4'-trimethoxystilbene, pinostilbene, tetramethoxystilbene, pentamethoxystilbene, and N-Hydroxy-N- (trimethoxphenyl)-trimethoxy-benzamidine and their and their dihydro-reduced equivalents. See Figures 2 and 3 for the names and aqueous solubilities of various resveratrol molecules.

[0052] As used herein, the term “resveratrol” refers to a compound seen in Figure 1 that may be synthesized, isolated, and purified from of a mixture of products produced in a host modified to express enzymes of the resveratrol biosynthetic pathway or that can be produced from natually occurring sources, such as grapes. “Resveratrol” further refers to derivatives and analogs thereof, including but not limited to forms of methylated, glycosylated and/or glucosylated resveratrol. For example, the resveratrol compound contemplated for use herein

may be produced *in vivo* through expression of one or more enzymes involved in the resveratrol biosynthetic pathway in a recombinant yeast or *in vitro* using isolated, purified enzymes involved in the resveratrol biosynthetic pathway, such as those described in WO2006/089898, WO2008/009728, WO2009/016108, WO2009/124879, WO2009/124967, WO2011/147818, which are incorporated by reference in their entirety. The resveratrol for inclusion in the feed, feed additives or water may be produced by recombinant microbial fermentation, including but not limited to fermentation extract, purified resveratrol, or dried fermentation cake from recombinant microbes capable of producing resveratrol. Resveratrol derived from fermentation of recombinant microbes is preferred not least because it is inherently free of emodin and hazardous levels of Polycyclic Aromatic Hydrocarbons (PAHs).

[0053] Therefore, resveratrol compositions as defined herein can differ chemically from other sources of resveratrol, such as extracts from plants and derivatives thereof, or may include such plant extracts and derivatives thereof in high purity.

[0054] As used herein, the terms “modified resveratrol,” “resveratrol derivative,” and “resveratrol analog” can be used interchangeably to refer to a compound that can be derived from resveratrol or a compound with a similar structure to resveratrol. For example, the terms “modified resveratrol,” “resveratrol derivative,” and “resveratrol analog” can refer to resveratrol-like molecules such as to glycosylated resveratrol molecules, methylated resveratrol molecules, or resveratrol molecules that are glycosylated and methylated.

[0055] As disclosed herein, the term “glycosylated resveratrol" refers to resveratrol glycosylated at the 3 hydroxyl group, or the 4’ hydroxyl group, or the 5 hydroxyl group of resveratrol, wherein glycosylation comprises covalently attaching one or a plurality of sugar or saccharide residues at one or more of the 3, 4’, or 5 hydroxyl groups of resveratrol. The saccharide moiety in each position can be independently zero, one, two, three, or multiple sugar residues, wherein all the sugar residues can be the same sugar residues or different sugar residues.

[0056] As used herein, the terms “saponin” and “saponins” are used interchangeably and may refer to a single saponins compound or to a blend of saponins. Saponins are amphipathic glycosides comprising a lipophilic triterpene derivatives and a hydrophilic glycoside moieties. Saponins are naturally present in some plants, with non-limiting but noteworthy examples present in the *Saponaria* genus (including the *Caryophyllaceae* family), the *Sapindaceae* genus (including the *Sapindus* family such as soapwort *Saponaria officinalis*), the *Aceraceae* genus (including the *Hippocastanaceae* family), and the *Polygala* genus of snakeroots and milkworts (including the Senega root, *Polygala senega*). Preferred sources of saponins suitable for use

in some aspects includes but are not limited to Quillay (*Quillaja saponaria)*, in Tea Seed (*Camellia oleifera*), in tea (*Camellia sinensis*), in liquorice (*Glychyrriza glabra*).

[0057] In some aspects the saponin is a plant steroid saponin, non-limiting examples of which may be found in *Yucca schidigera, Quillaia saponaria, Yucca schidigera, Trigonella foenum-graceum, Glycyrrhiza glabra, Saponaria officinalis, Gypsophylla paniculata, Smilax regelli* or *Trigonella foenum graecum*. Steroidal glycosides are naturally occurring sugar conjugates of C27 steroidal compounds. The aglycone of a steroid saponin is usually a spirostanol or a furostanol, or less commonly spirosolane or pregnane. The glycone parts of these compounds are mostly oligosaccharides, arranged either in a linear or branched fashion, attached to hydroxyl groups through an acetal linkage. Non-limiting plant steroid saponins include aspaoligonin A, aspaoligonin B, aspaoligonin C, atropuroside B, atropuroside F, degalactotigonin, dioscin, diosgenone, diosgenin, gracillin, icogenin, isoterrestrosin B, luciamin, methyl protogracillin, methyl protonegracillin, mimusopin, neosibiricoside C, neosibiricoside D, racemoside A, sarsapogenin, smilagenin, tribulosin, torvanol A, torvoside H, yuccaloeside B, yuccaloeside C, yayoisaponin A, yayoisaponin B, and yayoisaponin C.

[0058] In some aspects the saponin is a triterpene saponin (otherwise known as a triterpenoid saponin), non-limiting examples of which may be found in quillaja (also called quillaia, *Quillaja saponaria)*, Tea Seed (*Camellia oleifera*), tea (*Camellia sinensis*), quinoa or liquorice (*Glychyrriza glabra*). In some aspects the saponin is a glucoside saponin. In some aspects the saponin is a water soluble triterpene glucoside. In a preferred aspect, the saponin is quillaia saponin.

[0059] In one aspect the saponin is glycosylated quillaic acid, a hydrophobic triterpene of predominantly 30 carbon atoms of the D12-oleanane type. In one aspect the tripterpene saponins is soyasapogenol A and/or soyasapogenol B. In another aspect the saponin is solanine, the chemical structure of which is illustrated in Figure 2.

[0060] Depending on the plant species, saponins may be found at highest concentrations in the roots, blossom, fruit, stems, bark and leaves of the plant. Typical maximum saponin concentrations in the plant species mentioned herein range from 0.1% up to 2% dry matter, with the exceptions being *Yucca schidigera* and *Quillaia saponaria,* which may comprise saponins at concentrations of up to 10% total dry matter. There are only a handful of species possessing saponins in a concentration high enough to be effective for inclusion in animal or bird feed either directly or following low cost purification techniques. Further, the source plant may be slow growing, and sustainability issues are worsened if the saponins achieve highest concentration in the root, bark or stem of the plant. Blossoms and fruits may be easier to harvest in a sustainable manner, but seasonal variations ensure the saponin content may vary markedly

from year to location. It must also be noted that some plants with high saponin concentrations also contain molecules undesirable for inclusion in animal or bird feed. For example, several species of *Solanum* (such as bitter nightshade and black nightshade) contain saponins in their fruits and stems, but are poisonous and/or unpalatable to many warm blooded farmed animals. As a consequence of all of these considerations, the most preferred sources of saponins in some aspects are Tea Seed (*Camellia oleifera*), tea (*Camellia sinensis*), liquorice (*Glychyrriza glabra*), Mohave yucca (*Yucca schidigera*) or the soap bark tree, *Quillaja saponaria*, the inner bark, small stems and branches of which is milled and sold as Quillaia, China bark extract, Murillo bark extract, Panama bark extract, Quillaia extract, Quillaia bark extract, and Soapbark extract. *Yucca schidigera* and *Quillaia saponaria* have received from the Food and Drug Administration (FDA) a generally recognized as safe (GRAS) label, and are accepted as safe food, feedstuff and cosmetic ingredients in the United States.

[0061] In one aspect the inner bark of the *Quillaja saponaria* (*Quillaia* saponaria) plant may be used to form a concentrated component of animal feed or feed additive rich in saponins. In one aspect, the saponins may be provided as Quillaia, Quillaia extract, or as crushed, pressed *Quillaia* inner bark, shoots and/or stems, optionally milled or powdered. Although saponins may be extracted from the *Quillaja saponaria* (*Quillaia* saponaria) plant or any of the other saponin-producing plants listed above, saponins are just one category of a large number of molecules present in these raw materials and crude extracts derived therefrom. Additionally, the level of saponis in even the same sub-species or breed of *Quillaja saponaria* (*Quillaia* saponaria) will vary as a consequence of the age of the plants, the part of the plant harvested, the geographic region, altitude and climatic conditions experienced by the plants during their growth. Hence there may be some difficulty in consistently achieving the desired concentration and purity of saponins to meet the demand associated with the global farming and rearing of animals and birds.

[0062] In some embodiments, crude compositions comprising saponins suitable for incorporation into animal or bird feed or feed additives may therefore be derived from at least one of *Saponaria, Sapindaceae*, *Aceraceae* or *Polygala* stems, flowers, leaves, roots or inner bark, all preferably dried, or incorporated into a solution with water. Compositions with higher concentrations of saponins suitable for incorporation into animal or bird feed or feed additives may be achieved by immersing or washing these crude compositions with solvents suitable for use in feed or feed additives and then optionally further concentrated and/or selectively purified for thymol by evaporation, distillation, chromatography, or equivalent techniques. The resulting compositions comprising higher concentrations of saponins suitable for incorporation into animal or bird feed or feed additives may be present in the form of water extracts or alcohol extracts or combinations and blends thereof. Alcohol extracts may be preferred, since

resveratrol has significantly better solubility in alcohols such but not limited to ethanol, than its solubility in water. In some aspects, the saponins may be used to increase the water solubility of resveratrol by creating an emulsion suitable for inclusion in feed, feed additives, or drinking water.

[0063] According to some aspects, the saponins may be present in substantially pure form or be incorporated into the feed of feed additives to an effective concentration as an element of biological material comprising saponins such as at least one of Quillaia stems, Quillaia inner bark, Quillaia shoots (all preferably dried 0.1-0.3 dry wt%), or concentration extracts thereof.

[0064] Saponins may also be produced by recombinant microorganisms, such as recombinant *saccharomyces cerevisiae* as taught in *Arendt et al.* Metab Eng, 2017 and *Moses et al.* PNAS 2014, both of which are herein incorporated in their entirety by reference. According to some aspects, the saponins for inclusion in the feed, feed additives or water supplements may be produced by recombinant microbial fermentation, including but not limited to fermentation extract, purified saponins, or dried fermentation cake from recombinant microbes capable of producing saponins. In some aspects, the saponins and stilbenes (such as resveratrol or a derivative thereof) are produced by recombinant microorganisms and incorporated into the feed, feed additives or water supplements suitable for administration to animals, birds or fish. In a preferred aspect, the saponins and stilbenes (such as resveratrol or a derivative thereof) are produced by the same culture of recombinant microorganisms and incorporated into the feed, feed additives or water supplements suitable for administration to animals, birds or fish. In a preferred aspect, the saponins and stilbenes (such as resveratrol or a derivative thereof) are produced by the same recombinant microorganism (such as recombinant *Saccharomyces cerevisiae*) and incorporated into the feed, feed additives or water supplements suitable for administration to animals, birds or fish. In the above aspects, the saponins and stilbenes (such as resveratrol) may be present in the feed, feed additives or water supplements as purified or semi-purified compounds, yeast extracts, non-fermentive or direct fed microbials.

[0065] As used herein, the term “enzyme suitable for inclusion in animal or bird feed” means any enzyme that may be incorporated into animal or bird feed, feed additives, or water supplements. Enzymes suitable for inclusion in animal or bird feed are typically included to improve the efficiency of feed utilization (i.e. reduce the FCR) and/or to improve the health of the animal and/or to reduce the environmental impact of the animal or bird excreta. Non-limiting examples of enzymes that may be added to the animal or bird feeds, additives or supplements, or produced by the recombinant resveratrol and/or saponin-producing microorganisms to be incorporated into these compositions, includes without limitation one or more selected from the group comprising beta-glucanase, alpha-galactosidase, invertase, lactase, lipase,

phospholipase, acetyltransferase, phytase, cellulase, beta-galactosidase, protease, amylase, or xylanase.

Compositions

[0066] The active ingredients contemplated herein are used in the form of compositions. The active ingredients can be applied to feed, feed additives, drinking water or drink supplements, to form a comestible composition suitable for ingestion by animals and birds. The active ingredients can be applied, if desired, together with other carriers conventionally used in the formulation art of feed, feed additives and drink supplements, surfactants or other additives which aid application. Suitable carriers and additives can be solid or liquid and are the substances expediently used in the art of formulation, for example natural or regenerated mineral materials, solvents, dispersants, wetting agents, adhesives, thickeners, binders or attractants.

[0067] In one aspect, the resveratrol and saponin-containing compositions may comprise the fermentation cake of microorganisms capable of producing resveratrol and/or saponins. The microorganism engineered to produce resveratrol and/or saponins may be any food or feed-approved microorganism, preferably a yeast, such as baker's or brewer's yeast (*Saccharomyces cerevisiae*), *Kluveromyces marxianus*, *Candida utilis*. Incorporation of fermentation cake comprising resveratrol-producing microorganisms and/or saponin-producing microorganisms into animal or bird feed, feed additives or water supplement compositions has the advantage of providing additional nutrients, vitamins and minerals present in the fermentation broth or produced naturally by the microbes. In a preferred embodiment of this aspect, the resveratrol-producing recombinant microorganism is *saccharomyces cerevisiae* free of antibiotic markers and grown in a fermentation medium not comprising antibiotics. In another preferred embodiment of this aspect, the saponin-producing recombinant microorganism is *saccharomyces cerevisiae* free of antibiotic markers and grown in a fermentation medium not comprising antibiotics. In another preferred embodiment of this aspect, the saponins and resveratrol are produced in a recombinant microorganism which is *saccharomyces cerevisiae* free of antibiotic markers and grown in a fermentation medium not comprising antibiotics. *Saccharomyces cerevisiae* has been included in feed for many years, and is sometimes known as "Feed yeast". The use of feed yeast (an example of a "feed microorganism") has increased since the Bovine Spongiform Encephalopathy crisis, in consequence of the demand for "clean" protein sources which could not support the growth or reproduction of viruses or prions able to cross animal species barriers. *Saccharomyces cerevisiae* are now appreciated to have a high Protein Efficiency Ratio, have a high lysine content, are an excellent source of vitamin D and

further comprise significant concentrations of the nutrients glutathione, inositol and choline. Yeast beta-glucans and mannans also help stimulate the immune system of young and infants in many animal species.

[0068] In some aspects, the resveratrol and/or saponin-producing microorganisms may also be engineered to produce enzymes desirable for incorporation into animal or bird feeds, additives or supplements, such as to improve the efficiency of feed utilization or the health of the animal or bird.

[0069] In some aspects, the resveratrol and/or saponin-producing microorganisms (such as recombinant *cerevisiae*) are present as whole cells in "direct-fed microbial" compositions such as active dry yeast, yeast culture (such as molasses yeast condensed solubles). In some aspects, the resveratrol and/or saponin-producing microorganisms (such as recombinant *cerevisiae*) are present as whole cells that are heat treated, irradiated, lysed (such as by sonication or by hydrolysis), pasteurized, or in another way rendered "non-fermentive" so that the viability of recombinant microorganisms in the resulting composition is significantly reduced, preferably reduced to the extent that no viable recombinant microbes may be detected. The resveratrol, optionally with saponins, thymol and/or recombinantly produced enzymes suitable for inclusion in animal or bird feed may be added to the animal or bird feed, feed additive or water supplement as a "yeast extract" comprising concentrated soluble materials recovered from lysed yeast cells following fermentative growth.

[0070] In other embodiments of the invention, compositions contemplated herein can contain a carrier and at least about 0.0001%, or at least about 0.001%, or at least about 0.01%, or at least about 0.1%, or at least about 1%, or at least about 2%, or at least about 5%, or at least about 7.5%, or at least about 10%, or greater than about 10%, or greater than about 15%, or greater than about 20%, or greater than about 25%, or greater than about 50% by weight stilbene, such as resveratrol. In some applications, stilbene can be present in an amount that is greater than about 60%, about 70%, about 80%, about 90%, about 95% or about 99% by weight of the composition. In one example, the provided compositions contain stilbene in an amount at or about 0.0001% to at or about 2%, or about 0.001% to at or about 5%, or about 0.01% to at or about 75% by weight of the composition. In another example, a composition may contain stilbene in an amount of from at or about 1% to at or about 50% by weight of the composition. In another example, a composition may contain stilbene in an amount of from at or about 5% to at or about 40% by weight of the composition. In another example, a composition may contain stilbene in an amount of from at or about 10% to at or about 30% by weight of the composition. In another example, a composition may contain stilbene in an amount of from at or about 15% to at or about 25% by weight of the composition. In another example, a

composition may contain stilbene in an amount of from at or about 1% to at or about 90% by weight of the composition. In another example, a composition may contain stilbene in an amount of about 10%, or about 15%, or about 20%, or about 25%, or about 30%, or about 50% by weight of the composition. In another example, a composition may contain stilbene in an amount of up to about 99% or more by weight of the composition.

[0071] In one particular embodiment, a contemplated stilbene-containing composition, such as a resveratrol-containing composition is provided as a concentrate. For example, a stilbene-containing composition may be provided as a 20X, or a 10X, or a 5X, or a 3X concentrate that can be diluted by an end user with an appropriate solvent to achieve a 1X working concentration. Alternatively, a stilbene-containing composition may be provided to an end user at a 1X working concentration. However, any concentration is contemplated for use herein. For example, compositions provided as concentrates can be used without dilution at all or may be diluted from a highly concentrated concentrate (*e.g.*, about 20X to about 100X) to some multiple of concentration higher than 1X, such as 2X, 2.5X, 3X, etc. or can be used at a more dilute concentration, such as 1/2X, 1/4X, 1/10X, etc. While concentrates are more preferred as commercially available goods, the industry and end consumers typically apply dilute compositions to propagated plants, propagated plant material, materials and surfaces.

[0072] In another embodiment, a contemplated composition may be seen in Table 1, where ingredients can be measured in percent volume per volume, percent weight per volume, or percent by weight.

Table 1. Contemplated composition formulation.

Ingredient	Approximate %
Stilbene (such as resveratrol)	0.001 – 100
Saponins	0.001 – 100
Thymol	0 – 99.999
Additional active ingredients	0 – 99.999
Carrier	0 – 99.999
Additives	0– 99.999

[0073] In some aspects, the resveratrol and saponins are present in or contacted with the composition as a blend comprising 50wt% resveratrol to 50wt% saponins, or 30wt% resveratrol

to 70wt% saponins, or 20wt% resveratrol to 80wt% saponins, or 15wt% resveratrol to 85wt% saponins, or 10wt% resveratrol to 90wt% saponins.

[0074] Preferred inclusion rates of the blend of stilbene (such as resveratrol or a derivative thereof) and saponins include aggregate concentrations of less than 30ppm, 5 to 25ppm, 5 to 20ppm, 5 to 15ppm, or 5 to 10ppm.

[0075] In preferred aspects the resveratrol is produced by fermentation of recombinant microbes, which is more cost effective. Preferred production organisms include *Saccharomyces cerevisiae* or other yeasts.

[0076] In some aspects the resveratrol employed in the compositions and methods described herein may be resveratrol derivatives or other forms of resveratrol, particularly more water-soluble derivatives including but not limited to acetyl-resveratrol or pinosylvin.

[0077] Further examples of additional active ingredients include plant essential oil compounds or derivatives thereof. Examples include thymol, aldehyde C16 (pure), α-terpineol, amyl cinnamic aldehyde, amyl salicylate, anisic aldehyde, benzyl alcohol, benzyl acetate, cinnamaldehyde, cinnamic alcohol, carvacrol, carveol, citral, citronellal, citronellol, p-cymene, diethyl phthalate, dimethyl salicylate, dipropylene glycol, eucalyptol (cineole) eugenol, is-eugenol, galaxolide, geraniol, guaiacol, ionone, menthol, methyl salicylate, methyl anthranilate, methyl ionone, methyl salicylate, nootkatone, α-pheliandrene, pennyroyal oil perillaldehyde, 1- or 2-phenyl ethyl alcohol, 1- or 2-phenyl ethyl propionate, piperonal, piperonyl acetate, piperonyl alcohol, D-pulegone, terpinen-4-ol, terpinyl acetate, 4-tert butylcyclohexyl acetate, thyme oil, metabolites of trans-anethole, vanillin, and ethyl vanillin.

[0078] In another embodiment, a contemplated composition may include a stilbene, such as resveratrol, to additional active ingredient ratio of about 1:10, or about 1:8, or about 1:6, or about 1:4, or about 1:2, or about 1:1, or about 2:1, or about 4:1, or about 6:1, or about 8:1, or about 10:1. In some embodiments the additional active ingredient is thymol.

[0079] In other embodiments, compositions contemplated herein can include a stilbene in combination with saponins and optionally one or more additives, such as a fragrance, a preservative, or an attractant.

[0080] Carriers may be added to a composition in an amount of about 10%, or about 15%, or about 20%, or about 25%, or about 30%, or about 50% by weight of the composition. In some applications, a carrier can be present in an amount that is at or greater than about 60%, about 70%, about 80%, about 90%, about 95%, or about 99% by weight of the composition.

[0081] According to some aspects, carriers may be included as part of the feed or feed additive composition. Suitable carriers may be mineral carriers or vegetable carriers. Non-limiting examples of mineral carriers include sepiolite, zeolite (such as clinoptilolite), bentonite, calcium

carbonate, dicalcium phosphate, monocalcium phosphate, fine dried salt and diatomaceous earth. Although not inert, clay minerals may be suitable mineral carriers in some circumstances. Non-limiting examples of vegetable carriers include soy bean meal, maize flour, wheat flour and wheat middlings.

[0082] In other aspects, resveratrol and saponin-containing compositions can include a carrier, such as an aqueous liquid carrier, water, a saline, a gel, an inert powder, a zeolite, a cellulosic material, a microcapsule, an alcohol such as ethanol, a hydrocarbon, a polymer, a wax, a fat, an oil, and the like. Some carriers include time release materials where a stilbene-containing composition may be released over a period of hours, or days, or weeks. Suitable paniculate adsorptive carriers for granules are porous types, for example pumice, brick grit, sepiolite or bentonite, and suitable non-sorptive carrier materials are, for example, calcite or sand. Moreover, a large number of pregranulated materials of inorganic or organic nature can be used, such as, in particular, dolomite or comminuted plant residues.

[0083] Solvents suitable for incorporation into compositions according to some aspects of the current invention include but are not limited to alcohols and glycols and also their ethers and esters, such as ethanol, ethylene glycol, strongly polar solvents, or free vegetable oils, such as coconut oil or soya oil; water or solvents derived from natural products. In some aspects, alcohol solvents are preferred for resveratrol and/or thymol.

[0084] Depending on the nature of the active ingredients to be formulated, suitable surface-active compounds are non-ionic, cationic and/or anionic surfactants having good emulsifying, dispersing and wetting properties. Surfactants are also to be understood as meaning mixtures of surfactants.

[0085] Saponins are themselves natural surfactants, and this attribute can be enhanced by blending with additional surface-active compounds.

[0086] In some aspects, the saponins described herein may be used to aid the solubility of vitamin E in an aqueous preparation such as a supplement or additive composition suitable for inclusion in the feed or drinking water of a warm-blooded farmed animal or bird.

[0087] In some aspects, the saponins described herein may be used to aid the solubility of enzymes in an aqueous preparation such as a supplement or additive composition suitable for inclusion in the feed or drinking water of a warm-blooded farmed animal or bird. In some aspects, the saponins described herein may be used to decrease the intestinal viscosity of the alpha-glucan polysaccharides found in common feed grains (barley, oats, wheat). Reduced viscosity in the intestines of warm blooded farmed animals and birds (for example, chickens) is

important for reducing the frequency of constipation, thus reducing feed intake and concomitant weight gain.

[0088] Additives which aid application of compositions according to some aspects of the invention include natural or synthetic phospholipids from the series of the cephalins and lecithins, for example phosphatidylethanolamine, phosphatidylserine, phosphatidylglycerine, or lysolecithin.

[0089] In some aspects, feed-acceptable acids may be incorporated into the feed, feed additives or drinking water supplements. For example, to enhance shelf life and stability of some compositions described herein, it is advantageous to add up to approximately 5 wt% total of a feed acceptable acid such as citric acid, tartaric acid, propionic acid, sorbic acid or lactic acid, or a mixture thereof. In some aspects the feed-acceptable acids also have a positive influence on the efficacy of the product. Other appropriate preservatives may include calcium propionate, potassium sorbate or sodium benzoate.

Formulation examples

[0090] The feed-additives may be blended and packed at facilities using standard equipment known in the art as suitable for blending of vitamin and mineral premixes for animals. Non-limiting examples of feed additives include:

a. A blend comprising 15 grams resveratrol and 50 grams saponins (or saponin-rich extracts), which may be included in the feed at 65 grams per ton of feed.

b. A blend comprising 15 grams resveratrol and 25 grams saponins (or saponin-rich extracts), which may be included in the feed at 40 grams per ton of feed.

c. A blend comprising 10 grams resveratrol and 25 grams saponins (or saponin-rich extracts), which may be included in the feed at 35 grams per ton of feed.

d. A blend comprising 15 grams resveratrol and 15 grams saponins (or saponin-rich extracts), which may be included in the feed at 30 grams per ton of feed.

e. A premix blend comprising 15 grams resveratrol and 50 grams saponins (or saponin-rich extracts), which may be included in the feed at 65 grams per ton of feed.

f. A premix blend comprising 15 grams resveratrol and 25 grams saponins (or saponin-rich extracts), which may be included in the feed at 40 grams per ton of feed.

g. A premix blend comprising 10 grams resveratrol and 25 grams saponins (or saponin-rich extracts), which may be included in the feed at 35 grams per ton of feed.

h. A premix blend comprising 15 grams resveratrol and 15 grams saponins (or saponin-rich extracts), which may be included in the feed at 30 grams per ton of feed.

i. A soluble product containing 15 grams resveratrol, 50 grams saponins (or saponin-rich extracts) and 135 grams of sorbitol, which may be added to the drinking water via a 10% stock solution and added to the drinking water at 1%.

j. A soluble product containing 15 grams resveratrol, 25 grams saponins (or saponin-rich extracts) and 160 grams of sorbitol, which may be added to the drinking water via a 10% stock solution and added to the drinking water at 1%.

k. A soluble product containing 10 grams resveratrol, 25 grams saponins (or saponin-rich extracts) and 165 grams of sorbitol, which may be added to the drinking water via a 10% stock solution and added to the drinking water at 1%.

l. A soluble product containing 15 grams resveratrol, 15 grams saponins (or saponin-rich extracts) and 170 grams of sorbitol, which may be added to the drinking water via a 10% stock solution and added to the drinking water at 1%.

[0091] The following feed-additives, manufactured in their concentrated form on the basis of two or more elements (which may comprise insoluble and soluble variants) were blended and packed at facilities using approved equipment. The resulting compositions have also been blended with vitamins and minerals to produce premixes for animals and birds.

[0092] Non-limiting examples of feed additives include:

a. 5-30 grams 98% pure resveratrol and 5-30 grams saponins (or saponin-rich extracts) per ton of feed which may be incorporated into standard bird or animal feed at 15-30 grams per ton of feed.

b. 5-20 grams 98% pure resveratrol and 5-30 grams saponins (or saponin-rich extracts) which may be incorporated into feed at 15 grams per ton of feed.

c. 5-20 grams 98% pure resveratrol and 5-20 grams saponins (or saponin-rich extracts) blended, and 15g of the blend mixed in to 485 grams clay mineral to provide a premix which may be incorporated into feed at 500 grams per ton of feed.

A soluble product containing about 7.5 grams 98% pure saponins (or saponin-rich extracts) and 7.5 grams thymol and 135 grams of sorbitol were blended and made up to a 10% stock solution in water, suitable for addition to the drinking water of birds or animals at 1% or less. In some aspects the 10% stock solution may be added to 1,000-3,000L drinking water. In some aspects, the resveratrol and saponins are present in or contacted with the composition as a blend comprising 50wt% resveratrol to 50wt% saponins, or 30wt% resveratrol to 70wt% saponins, or 20wt% resveratrol to 80wt% saponins, or 15wt% resveratrol to 85wt% saponins, or 10wt% resveratrol to 90wt% saponins.

[0093] Preferred inclusion rates of the blend of stilbene (such as resveratrol or a derivative thereof) and thymol include aggregate concentrations of less than 30ppm, 5 to 25ppm, 5 to 20ppm, 5 to 15ppm, or 5 to 10ppm.

[0094] Preferred inclusion rates of the blend of stilbene (such as resveratrol or a derivative thereof) are from about 5 ppm to about 30 ppm and inclusion rates of the saponins are from about 5 ppm to about 500 ppm.

Methods

[0095] According to some embodiments of the current invention, compositions comprising active ingredients may be applied once per day, once per week, twice per week, once per two weeks, once per month, once per two months, once per three months, or once per lifecycle of the object to which the composition is being applied. Compositions according to aspects of the current invention may be employed as pure active ingredients or, preferably, together with the auxiliaries conventionally used in the art of formulation and are therefore processed in a known manner to give, for example, emulsion concentrates, spreadable pastes, ready-to-spray or ready-to-dilute solutions, dilute emulsions, wettable powders, soluble powders, dusts, granules, or encapsulations, for example in polymeric materials. The methods of application, such as spraying, atomizing, dusting, scattering, brushing on, submerging, coating, pouring or rubbing, and the type of composition are selected to suit the intended aims and prevailing circumstances.

[0096] A preferred method of applying a mixture of active ingredients comprising in each case at least one of the active ingredients

[0097] Compositions as described herein may be introduced to warm blooded mono-gastric farmed animals and birds at any time of the life cycle (i.e. to subjects of all ages), including but not limited to piglets, lactating sows, grower pigs and finishing pigs. In some aspects, compositions as described herein are preferably used in the finishing of commercially reared animals or birds. In some aspects, compositions as described herein are administered or incorporated into the feed, feed supplements or drinking water during the entire growth of commercially reared animals or birds. As a non-limiting example, the compositions described herein may be administered to broiler chickens from time of hatching until slaughter, typically at 28 to 33 days in Asia but often at 35, 42, or 56 days elsewhere.

[0098] Generally and without limitation, compositions contemplated herein can be in the form of an aqueous liquid, an oil-based liquid, a concentrated liquid, a gel, a foam, an emulsion, a slurry, a paint, a clear coat, a wax, a block, a pellet, a puck, a granule, a powder, a capsule, a

vesicle, an effervescent tablet, slow release tablet, an impregnated dissolvable sheet or film, an impregnated material, and combinations thereof.

[0099] In some embodiments, compositions comprising stilbene (such as resveratrol) or a derivative thereof, and saponins, may be administered directly to the feed, food or drinking water of piglets to be treated from the time they are freshly weened to until they achieve at least 30kg in weight. In other embodiments compositions comprising stilbene (such as resveratrol) or a derivative thereof, and thymol, may be administered directly to the feed, food or drinking water of finisher pigs to be treated from the time they have achieved at least 75kg in weight (typically approximately 4 weeks before slaughter) until they are slaughtered.

[00100] In some embodiments, compositions comprising stilbene (such as resveratrol) or a derivative thereof, and saponins, may be administered directly to the feed, food or drinking water of starter, grower, or finisher broiler chickens.

[00101] In some embodiments, compositions comprising a stilbene (such as resveratrol) and at least one triterpene saponins (such as a blend of triterpene saponins from *Quillaia saponaria*) with a carrier selected from one or more of a sepiolite, a clinoptilite and/or diatomaceous earth may be administered to farmed animals, birds, fish or shellfish at the following dosages:

Piglets, growers	500 grams/ton of feed (500 ppm)
Finisher pigs (final 4 weeks before slaughter)	500 - 1000 grams/ton of feed (500 - 1000 ppm)
Broilers	500 grams/ton of feed (500 ppm)
Egg-laying hens	500 grams/ton of feed (500 ppm)
Shrimps	500-1000 grams/ton of feed (500-1000 ppm)
Fish	500-1000 grams/ton of feed (500-1000 ppm)

Manufacture, Packaging and Finish

[00102] The compositions disclosed herein may be included in dry or wet feeds, or in the animals' drinking water.

[00103] In some aspects the resveratrol and saponins may be added separately or together to the drinking water, feed, premixes, supplements or concentrates described herein.

[00104] In some aspects, the saponins present in the resveratrol and saponins containing compositions described herein has natural antimicrobial properties, so may added with or without sanitisation, pasteurisation, sterilisation (such as microfiltration or heat treatment). In some aspects, pelletized feed suitable for use as described herein may be undergo a sufficient heat treatment during the palletisation process that a subsequent sterilisation step is optional.

[00105] In the aspects relating to administration via the feeds, the additives may in their concentrated forms be included via vitamin and mineral-premixes or concentrates suitable for addition to feeds. Less concentrated formulations comprising the blend of active ingredients and optional additives may be included via base-mixes, or directly into the feeds at a feed-mill, or at a home-mixing farm.

Application and use

[00106] In some aspects, feeding broiler chickens with feed compositions comprising 15 ppm of compositions rich in resveratrol and thymol results in the broilers reaching a higher live-weight.

[00107] In some aspects, feeding broiler chickens with feed compositions in which compositions rich in resveratrol and saponins may be included at a combined rate of about 15ppm. This blend was found to result in the broilers reaching a live-weight of 100 grams more than broilers receiving standard feed by day 35 after hatching. Typically, broilers that are slaughtered at 35 days of age will have consumed the following percentage of total feed at each stage of their growth:

Day 0 - 10: 10%

Day 11 - 21: 28%

Day 22 - 35: 62%

[00108] In some aspects, feeding broiler chickens with feed compositions comprising compositions comprising 15 ppm of extracts rich in resveratrol and saponins results in the broilers reaching a live-weight of 150 grams more than broilers receiving standard feed by day 42 after hatching. Typically, broilers that are slaughtered at 42 days of age will have consumed the following percentage of total feed at each stage of their growth:

Day 0 - 10: 6%

Day 11 - 21: 19%

Day 22 - 35: 45%

Day 36 - 42: 30%

[00109] In some aspects, feeding newly weaned piglets with a feed compositions comprising 15 ppm of extracts rich in resveratrol and saponins results in the piglets reaching a live weight of 800 grams more than piglets receiving standard feed by day 14 after weaning.

Examples

EXAMPLE 1: Effects of the combination of the combination of Resveratrol and Saponins in the growth of porcine livestock.

[00110] 288 newly weaned piglets were distributed by weight and sex into 4 equivalent groups. Each group was divided into two pens with a shared feed dispenser (as shown in Figure 3). The study was carried out in a farm in Tissø, Vestsjælland, Denmark

[00111] For the first 14 days, the piglets were fed *ad libitum* with the same standard feed plus the additives described below and free access to water.

[00112] The four groups in the trial were:

Control group (T0 or Control): No inclusion of additive

Trial group 1 (T1 or Res30): Inclusion of 30 ppm R (resveratrol)

Trial group 2 (T2 or RSAP15): Inclusion of 15 ppm R (resveratrol) and 50 ppm saponins

Trial group 3 (T3 or RSAP30): Inclusion of 30 ppm R (resveratrol) and 50 ppm saponins

[00113] The results, after 14 days, are shown in Table 1.

Table 1: Results after 14 days

Trial data	T0	T1	T2	T3	Index T1/T0	Index T2/T0	Index T3/T0
Number of pigs	72	72	72	72	100	100	100

Number of pig days	1008	1008	1008	1008	100	100	100
Total start weight, kg	425	428	419	420	100.7	98.6	98.8
Av. start weight, kg	5.9	5.9	5.8	5.8	100.7	98.6	98.8
Total weight 14 days, kg	609	598	596	592	98.2	97.9	97.2
Av. weight 14 days, kg	8.5	8.3	8.3	8.2	98.2	97.9	97.2
Weight gain/pig, kg	2.6	2.4	2.5	2.4	92.6	96.1	93.4
Total feed intake, kg	218	190	177	189	87.2	81.2	86.7
ADG, g	**183**	**169**	**176**	**171**	**92.4**	**96.2**	**93.5**
ADFI, g	**216**	**189**	**176**	**188**	**87.1**	**81.2**	**86.7**
FCR (grams/grams)	**1.19**	**1.12**	**1**	**1.1**	**94.3**	**84.4**	**92.7**
Pigs removed/dead	0	0	0	0	-	-	-

ADG = Average daily gain, ADFI = Average daily feed intake, FCR = Feed conversion ratio

[00114] The combination of resveratrol and saponins has a distinct, positive effect on the efficiency of the piglets' feed-conversion. No pigs died during the first trial period.

[00115] The feed intake was highest for the Control-group, followed by the T1 and T3 treatments, being lower in T2. The weight gain was also affected in the test groups but to a lower extent than the feed intake.

[00116] The most efficient feed conversion ratio was seen for group T2 followed by T1 and T3 with the control group being the less efficient.

[00117] For the next 7 days, the piglets were fed *ad libitum* with the same standard feed and free access to water.

[00118] After the defined trial-period, the administration of the trial-products was discontinued, and the piglets in all four groups involved in the trial were weighed again 7 days after the formal trial had concluded.

[00119] The results of weighings are shown in Table 2.

Table 2: Results from the last week of the trial - from day 14 - 21

Trial data	T0	T1	T2	T3	Index T1/T0	Index T2/T0	Index T3/T0
Number of pigs	72	72	72	72	100	100	100
Number of pig days	504	504	504	504	100	100	100
Total weight day 14, kg	609	598	596	592	98.2	97.9	97.2
Av. weight day 14, kg	8.5	8.3	8.3	8.2	98.2	97.9	97.2
Total weight day 21, kg	809	795	810	822	98.3	100.1	101.6
Av. weight day 21, kg	11.2	11	11.3	11.4	98.2	100.1	101.6
Weight gain/pig, kg	2.8	2.7	3	3.2	98.2	106.8	115.1
ADG, g	397	391	425	456	98.5	107	115
Pigs removed/dead	**0**	**0**	**0**	**0**	**-**	**-**	**-**

[00120] The feed intake was not recorded for the last 7 days so ADFI and FCR was not calculated.

[00121] No pigs died during the trial period.

[00122] The weight gain of groups T3 and T2 was significantly higher than the Control and T1 groups.

[00123] The overall results, after 21 days, are shown in Table 3.

Table 3: Results from the last week of the trial - from day 14 - 21

Trial data	T0	T1	T2	T3	Index T1/T0	Index T2/T0	Index T3/T0
Number of pigs	72	72	72	72	100	100	100
Number of pig days	1008	1008	1008	1008	100	100	100
Total start weight, kg	425	428	419	420	100.7	98.6	98.8
Av. start weight, kg	5.9	5.9	5.8	5.8	100.7	98.6	98.8
Total weight 21 days, kg	809	795	810	822	98.3	100.1	101.6
Av. weight 21 days, kg	11.2	11	11.3	11.4	98.2	100.1	101.6
Weight gain/pig, kg	5.3	5.1	5.4	5.6	95.5	101.7	104.7
ADG, g	254	243	259	266	95.6	101.8	104.7
Pigs removed/dead	**0**	**0**	**0**	**0**	**-**	**-**	**-**

Other observations:

[00124] During the first 14 days of treatment, the trial host observed that the manure in treatment groups T2 and T3 were darker than the negative control and typical manure from standard feeds. Dark manure is associated with lower levels of ammonia (solid/volatile) in the manure and therefore a higher protein uptake.

Conclusions:

[00125] The combination of resveratrol and saponins has beneficial effects on the efficiency of newly-weaned piglets' feed conversion ratio of porcine livestock.

[00126] During the first 14 days the addition of the combination of resveratrol and saponins improved the feed conversion ratio, mainly by reducing ADFI while maintaining ADG close to the control group.

[00127] In the period from days 14 to 21, the groups that received the combination of resveratrol and saponins during the first 2 weeks, significantly improved ADG.

[00128] After 21 days (14 with treatment + 7 without treatment) the animals in groups T2 and T3 reached the higher weight while consuming significantly less food in the first 2 weeks.

[00129] Given the observation of darker manure in groups T2 and T3, it is expectedx that the combination of resveratrol and saponins would exert even more marked benefits when added to feeds with a relatively poorer protein content, thus permitting the more efficient use of a wider diversity of feeds. Also, the lower levels of ammonia in the manure present relevant environmental benefits in terms of less stress to the farmed animals and less environmental pollution.

[00130] Hence at least the following advantages were observed in combination applications of saponins and resveratrol (i) higher weight gain, (ii) more efficient feed intake, (iii) improved utilization of protein in the feed with concomitant reduction in the nitrogen content of the manure.

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Claims

1. A composition comprising between 5 and 100ppm of a blend comprising at least one saponin and at least one stilbene, suitable for inclusion within or addition to a feed, feed additive, drinking water or drink supplement of a farmed animal or bird, a companion animal or bird, livestock, a domesticated animal or bird, or an animal or bird bred for competition.

2. A composition according to claim 1 wherein the blend comprising at least one saponin and at least one stilbene has a saponin to stilbene ratio of between 5:1.5 and 5:3 by weight.

3. A composition according to claim 1 or 2 wherein the composition comprises a combined concentration of at least one saponin and at least one stilbene of approximately 500ppm.

4. A composition according to any of claims 1 to 3 wherein the composition comprising stilbene comprises a recombinant microorganism capable of producing the stilbene, or as a crude fermentation cake produced during the fermentation of said recombinant microorganism, or as lysed cellular extracts of a microorganism capable of producing the stilbene, or as stilbene purified therefrom to at least 50% purity, at least 80% purity, at least 90% purity, or at least 98% purity.

5. A composition according to claim 4, wherein the recombinant microorganism capable of producing the stilbene is a yeast.

6. A composition according to claim 5, wherein the recombinant yeast capable of producing the stilbene is *Saccharomyces cerevisiae.*

7. A composition according to any of the preceding claims, wherein the composition further comprises at least one additional ingredient selected from thymol, solvents, surfactants, antioxidants or one or more enzymes with an activity selected from beta-glucanase, alpha-galactosidase, invertase, lactase, lipase, phospholipase, acetyltransferase, phytase, cellulase, beta-galactosidase, protease, amylase, or xylanase.

8. A method of at least one of increasing the Average Daily Gain or reducing the Feed Conversion Ratio or reducing the ammonia content in the manure, of animals or birds by:

i. contacting any of the compositions of claims 1 to 7 with the feed, feed additives, drinking water or drink supplements, to form a comestible composition comprising resveratrol and at least one saponin suitable for ingestion by said animal or bird, and

ii. administering the comestible composition of step (i) to the animal or bird at least once per day for at least 10 days.

9. Use of a composition of any of claims 1 to 7 to increase and/or homogenize the Average Daily Gain and/or final live weight of farmed animals or birds, companion animals or birds, livestock, domesticated animals or birds, or animals or birds bred for competition.

10. A method or use according to any of the preceding claims, wherein the animal or bird is a monogastric animal or bird.

11. A method or use according to any of the preceding claims, wherein the monogastric animal or bird is a chicken, turkey, goose, duck, pigeon, pig, horse, sheep, rabbit, dog or cat.

12. A method or use according to claim 10, wherein the monogastric animal is a farmed piglet, a finisher pig, a broiler chicken, or a laying chicken.

13. A method or use according to claim 11 wherein the composition comprising at least one saponin and at least one stilbene increases the homogeneity of final live weight of a group of piglets, finisher pigs, or broiler chickens compared to a group not having received the composition.

14. A method or use according to any of claims 8 to 7, wherein the animal or bird is a ruminant.

15. A composition, method or use according to any of the preceding claims, wherein the stilbene is resveratrol, pinosylvin, or a methylated or glycosylated derivative thereof.

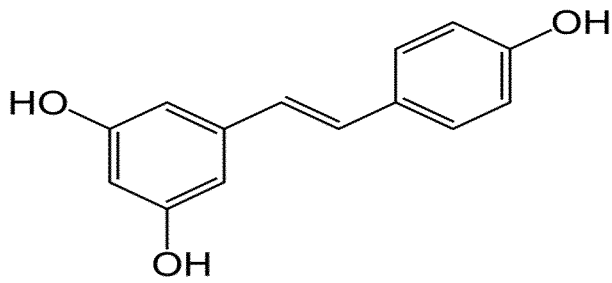


Figure 1. Chemical structure of trans-resveratrol.

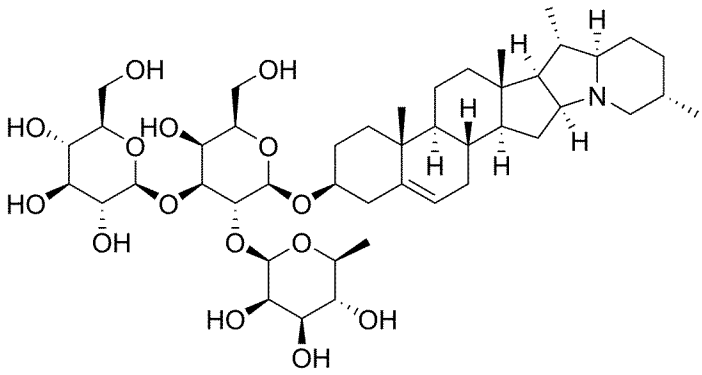


Figure 2: Chemical structure of solanine.

		RSAP30		Control							
13	14	15	16	17	18	19	20	21	22	23	24
12	11	10	9	8	7	6	5	4	3	2	1
		RSAP15		Res30							

Figure 3: The layout of the building where the pigs were housed in Example 1.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2018/060288

A. CLASSIFICATION OF SUBJECT MATTER
INV. A23K20/10 A23K20/111 A23K20/121 A23K50/30
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A23K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, FSTA, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2015/342901 A1 (KO WON HWA [KR] ET AL) 3 December 2015 (2015-12-03) paragraphs [0001], [0004] - [0013] examples 1-5	1-3,7,15
X	US 2015/250842 A1 (CALABOTTA DAVID [US] ET AL) 10 September 2015 (2015-09-10) paragraphs [0002], [0003], [0004], [0005], [0010], [0097], [0098], [0109] paragraph [0141] table 2	1,3, 7-12,14, 15

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 June 2018	20/06/2018

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Couzy, François

1

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ALAGAWANY ET AL: "Mechanisms and Beneficial Applications of Resveratrol as Feed Additive in Animal and Poultry Nutrition: A Review", INTERNATIONAL JOURNAL OF PHARMACOLOGY, vol. 11, no. 3, 1 January 2015 (2015-01-01), pages 213-221, XP55473841, the whole document	1-15
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A	Y.H. SHI ET AL: "Effects of alfalfa saponin extract on growth performance and some antioxidant indices of weaned piglets", LIVESTOCK SCIENCE, vol. 167, 1 September 2014 (2014-09-01), pages 257-262, XP055482971, NL ISSN: 1871-1413, DOI: 10.1016/j.livsci.2014.05.032 abstract table 2	1-15
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Information on patent family members

International application No
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