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Plant Bioactive Compounds in Pre- and Postharvest Management for Aflatoxins Reduction

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Aflatoxins (AFs) are secondary metabolites produced by *Aspergillus* spp., known for their hepatotoxic, carcinogenic, and mutagenic activity in humans and animals. AF contamination of staple food commodities is a global concern due to their toxicity and the economic losses they cause. Different strategies have been applied to reduce fungal contamination and AF production. Among them, the use of natural, plant-derived compounds is emerging as a promising strategy to be applied to control both *Aspergillus* spoilage and AF contamination in food and feed commodities in an integrated pre- and postharvest management. In particular, phenols, aldehydes, and terpenes extracted from medicinal plants, spices, or fruits have been studied in depth. They can be easily extracted, they are generally recognized as safe (GRAS), and they are food-grade and act through a wide variety of mechanisms. This review investigated the main compounds with antifungal and anti-aflatoxigenic activity, also elucidating their physiological role and the different modes of action and synergies. Plant bioactive compounds are shown to be effective in modulating *Aspergillus* spp. contamination and AF production both *in vitro* and *in vivo*. Therefore, their application in pre- and postharvest management could represent an important tool to control aflatoxigenic fungi and to reduce AF contamination.

Keywords: *Aspergillus*, aflatoxins, reduction, bioactive compounds, plant extracts

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INTRODUCTION

Aflatoxins (AFs) are toxic secondary metabolites, mainly produced by *Aspergillus* spp., which are recognized as human carcinogens (AFs of the B and G series) and possible carcinogens (AFs of the M series). They represent a great health concern (Kumar et al., 2017). Toxic outcomes, also known as aflatoxicosis, may include liver cancer, hepatotoxicity, immune system depression, and impaired growth both in humans and animals (IARC, 2012). AF maximum limits are regulated in Europe; products exceeding the maximum levels cannot be placed on the market nor mixed with uncontaminated ones (European Commission, 2006). From a chemical point of view, AFs (**Figure 1**) are difuranocoumarins composed of two furan rings arranged to a coumarin moiety in a rigid and planar structure (Loi et al., 2017). The high chemical stability endows them with high resistance to heat treatments, extreme pH values, high pressures, and mild (food grade) chemical treatments. As a result, the contamination persists in processed products, including those deriving from animals. Meat, milk, and eggs may also be contaminated with

AF metabolites, mainly originating from *in vivo* hydroxylation reactions (AF of the series M, aflatoxicol, aflatoxin Q_1, and aflatoxin P_1). AF contamination is a major problem in tropical and subtropical regions, where the environmental conditions are extremely favorable to fungal growth and AF production. However, in the last years, also Mediterranean areas have suffered from severe AF contamination due to climate change, temperature rise, and recurrent droughts (Moretti et al., 2019). AF management is a complex task, requiring actions at every stage of the supply chain (**Figure 2**). The application of the Good Manufacturing Practices (GAPs), i.e., crop rotation, the use of fungicides, and resistant varieties, is the first critical practice to prevent and reduce fungal contamination. However, the GAPs alone are not sufficient to avoid AF contamination, as it may depend upon several biotic and abiotic factors, also during storage (Mahuku et al., 2019). Therefore, the postharvest management is essential to manage AF contamination throughout the whole supply chain (Leslie and Logrieco, 2014).

Aspergillus spp. contamination can be detected in samples by several approaches. A basic microbiological diagnosis with chromogenic substrates was developed for the detection of toxigenic fungi, including *Aspergillus flavus*, *Aspergillus carbonarius*, and *Aspergillus ochraceus*. The great advantage is the use of basic laboratory equipment, a relatively low cost, and time for analysis (48–72 h). However, being a very generic growth test, it can be used only as a rapid screening test (Jefremova et al., 2016). On the contrary, advanced molecular PCR-based tools can be used to tackle conserved genes in *Aspergillus* spp. and AF biosynthetic gene cluster in contaminated materials (Moretti and Susca, 2017).

Controlling humidity, temperature, and moisture are among the most effective management strategies to cope with fungal spoilage and AF production during the storage and transport of susceptible commodities (Neme and Mohammed, 2017). Physical methods, such as sorting, dehulling, cleaning, and milling, are widely used to remove highly contaminated fractions from cereals during processing. Other physical methods include the use of microwave, UV, pulsed light, electrolyzed water, cold plasma, ozone, and irradiation. Despite their potentialities, their use is still limited due to the high technology cost and the residual toxic potential (Mahato et al., 2019).

Biological methods rely on the application of microorganisms (Liuzzi et al., 2017), pure enzymes (Loi et al., 2018), or enzyme extracts (Branà et al., 2020) able to degrade and, possibly, detoxify mycotoxins. In Europe, they can be authorized as postharvest treatments in feed, as long as safety, efficacy, and non-interference with feed nutrients is proved (Commission Regulation (EU) 2015/786, 2015).

The use of chemicals to prevent fungal growth in the field, in food, and feed products is a common practice worldwide. The use of fungicides and artificial preservatives has raised concern in consumers, researchers, and stakeholders because of the possible residual toxicity, carcinogenicity, and environmental pollution. The possible development of new resistant fungal strains is also a matter of great concern. Therefore, the use of natural compounds may encounter higher consumers' and stakeholders' acceptability (Onaran and Yanar, 2016). Bioactive compounds deriving from plant metabolism belong to greatly diverse chemical groups and possess different biochemical and physiological roles. Therefore, they are considered versatile molecules. Indeed, determining the exact and univocal function of secondary metabolites in plants is a difficult task.

Nonetheless, they share common antimicrobial (Bassolé and Juliani, 2012), antifungal (Tabassum and Vidyasagar, 2013), antioxidant properties (Miguel, 2010), and the capability of improving the postharvest management of vegetable crops (Sivakumar and Bautista-Baños, 2014). Moreover, particular attention is paid to these molecules as bioactive compounds in the human diet because of their high antioxidative capacity (Pisoschi et al., 2016).

Despite their potentialities having been widely investigated in the past, their application as AFs control agents in pre- and postharvest remains still poorly explored. Bioactive compounds have been widely used to inhibit *Aspergillus* growth at different levels (mycelia growth, spore production, germ tube formation), to inhibit the secondary metabolism and AFs production. In addition, their direct use was also found to degrade AFs and, in some cases, detoxify them.

BIOACTIVE COMPOUNDS IN PLANT METABOLISM

Plants are the richest source of bioactive compounds. Bioactive metabolites are classified into primary or secondary metabolites, depending on their functional role (Sharma et al., 2019). Plants and fungi produce thousands of secondary metabolites according to the physiological stage, tissue localization (floral and non-floral leaves, fruits, or bark), environmental conditions, and other biotic or abiotic stress. These compounds may be involved in the primary physiological function of the cell; they may participate in the control of cell growth and cell development, acting as plant growth substances, i.e., plant hormones. Among them, ethylene, auxin, gibberellins, abscisic acid, cytokinins, brassinosteroids, and polyamines are the most important ones (Depuydt et al., 2016). Nevertheless, their main function is ecological, especially with regards to the plant defense against herbivores, bacteria, and fungi (Mithöfer and Maffei, 2017).

Plants cope with pathogen attacks by different types of defense mechanisms, based on either anatomical or biochemical features (passive and constitutive defense), or active changes induced by pathogens (active and inducible defense). In some cases, like for terpenes, compounds can be secreted in low basal amounts constitutively, and expression can be triggered to produce higher amounts upon tissue damage or pathogen attack. Passive or constitutive defense compounds include glucosides, saponins, antifungal proteins, inhibitors of enzymes, and antifeedants, while inducible molecules include phytoalexins, pathogen-related (PR) proteins, chitinases, and glucanases (Walters, 2011).

Metabolites involved in the defense mechanism may occur in glycosylated or conjugated forms, which allow the plant to synthetize and store them in a non-toxic form. The conjugation or their specific localization (i.e., in the vacuoles or other

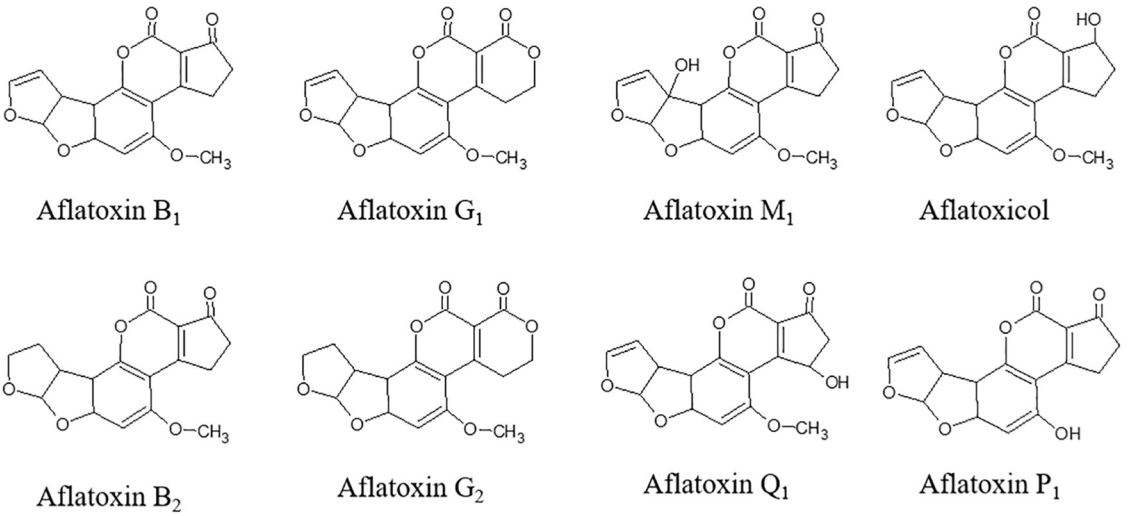

FIGURE 1 | Chemical structure of aflatoxins and their metabolites.

subcellular compartments) are strategies to avoid autoallelopathy and to produce active forms quickly and only when needed (Chaves Lobón et al., 2019).

Conversely, the *de novo* synthesis of antifungal molecules is also observed during the infection process in many plants. These substances are called phytoalexins, and they are similar to the constitutive antifungal toxins, although they show a more lipophilic character. Plants can also produce compounds with animal hormonal activity, the phytoecdysones, which can alter or cause precocious insect development. Finally, they may have a role in establishing the symbiotic processes with beneficial fungi and lichens (Ghasemzadeh and Ghasemzadeh, 2011).

Bioactive compounds can be extracted by different techniques: Soxhlet extraction, maceration, and hydrodistillation are classically used. The use of ultrasounds, microwaves, electric fields, high pressures, or supercritical fluids have been investigated to reduce the use of solvents and apply gentler extraction conditions (Azmir et al., 2013; Giacometti et al., 2018). Water traces can be removed to obtain a concentrated extract, also referred as to essential oil (EO). On the basis of the biosynthetic origin, secondary metabolites can be divided into three main groups: (i) phenolics, (ii) terpenes, and (iii) nitrogen-containing compounds. With regards to the antifungal and antiaflatoxin activity, the most important bioactive secondary compounds are reported in **Figure 3**.

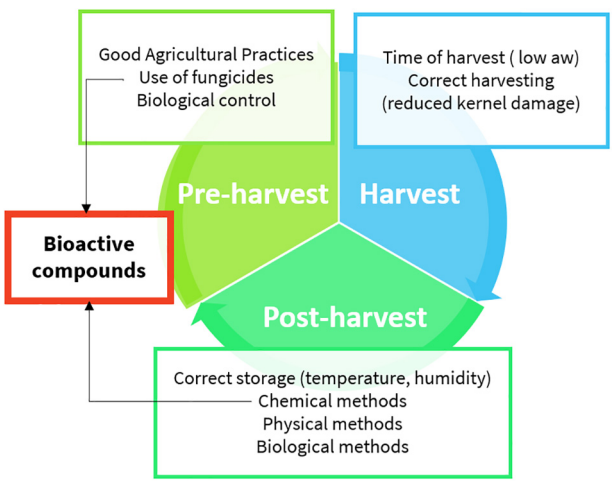

FIGURE 2 | Aflatoxin management practices (details are provided in the text).

(i) Phenolic Compounds

The term phenolic compounds generally includes compounds bearing one or more hydroxylated aromatic rings and are subgrouped into phenolic acids, stilbenes, flavonoids, lignans, and ellargic acids. The flavonoids subgroup comprises a wide variety of simple compounds like anthocyanins, flavonols, chalcones, flavanones, flavones, and isoflavones or complex ones, such as condensed tannins (Zhang and Tsao, 2016). Thanks to their hydroxyl and carboxyl moieties, polyphenols act as antioxidants. They modulate the cellular redox status by directly quenching free radicals and chelating metal ions (promotors of oxidative reactions). They also activate redox-sensitive transcription factors for the antioxidative enzymes (superoxide dismutase, catalase, and glutathione peroxidase) (Upadhyay and Dixit, 2015). Protein binding and inhibition is mediated by hydrogen bonds between hydroxyl moiety of phenols and the carboxyl and thiol groups of proteins. Conversely, the aromatic ring is able to interact with proteins through van der Waals (hydrophobic) interaction.

Structure–activity relationships of two phenol derivatives (cinnamaldehyde and eugenol) were studied on two phytopathogenic fungi, namely, *Rhizoctonia solani* and

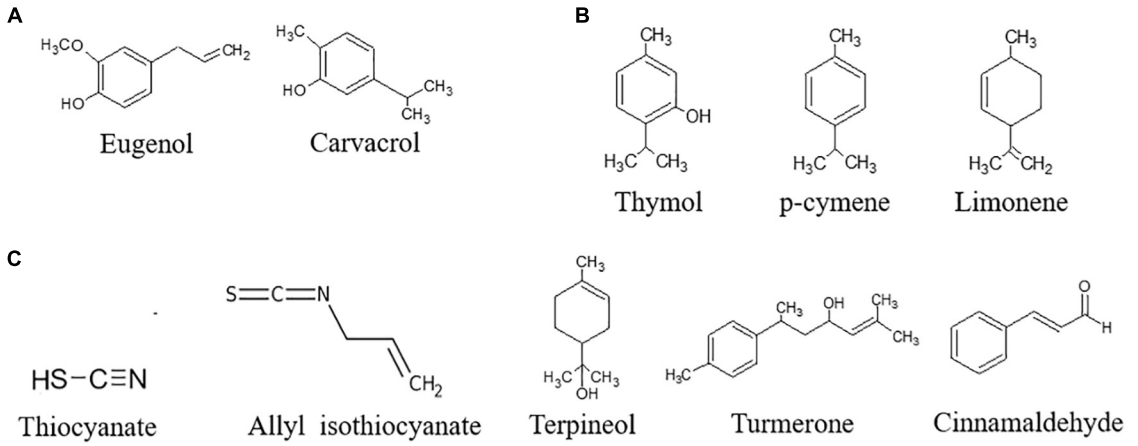

FIGURE 3 | Chemical structure of the most important bioactive secondary compounds with antifungal and antiaflatoxin activity. **(A)** Phenols, **(B)** Terpenes, **(C)** N-containing compounds.

Fusarium oxysporum. Phenol antifungal activity was shown to depend on the chemical structure. In particular, aldehydes, acid groups, conjugated double bonds, and the length of CH chain outside the ring have increased the antifungal activity (Xie et al., 2017). While aldehydes and acid groups may be more prone to react with amino acid residues of proteins through hydrogen bonds and induce conformational modification because of the proton release ability, the length of the CH chain increases hydrophobicity, a major determinant of phenol capability to enter the plasma membrane (Ben Arfa et al., 2006; Dambolena et al., 2011).

(ii) Terpenes

Terpenes are volatile compounds deriving from the condensation of two or more isoprene molecules. They represent the largest class of plant compounds, with more than 40,000 different chemical structures. They are usually synthetized and stored in trichomes or secretory glands to be secreted constitutively or released as a consequence of tissue damages. Their function in plant metabolism is extremely diverse. Terpenes act as radical scavenging molecules against UV light damage and other environmental stresses. The double bonds can absorb high-energy radiation or scavenge free radicals, functioning as a first defense mechanism. Nonetheless, not all terpenes have a defensive function. Volatile terpenes are generally released constitutively to act as attractants to pollinators and symbionts, repellents to herbivores, or as signaling molecules to other plants or plant tissues. Polyisoprene intermediates are used in the post-translational modification of prenylated proteins (Pichersky and Raguso, 2018). Limonene, carvone, carvacrol, linalool, thymol, terpineol, myrcene, linalool, and pinene are the most important ones, with regards to the antifungal activity against *Aspergillus* spp. The latter activity is mainly due to their lipophilic nature, which allows them to enter the cell and interact with the cellular and mitochondrial membranes, and cause alteration in cell permeability and electrochemical potential (Tian et al., 2012b).

(iii) Nitrogen-Containing Compounds

Nitrogen-containing compounds are a heterogeneous group, which share the presence of at least one nitrogen atom in their chemical structure: glucosinolates, alkaloids, and cyanogenic glucosides are the main classes. All of them have defensive functions, but only glucosinolates have been recently exploited as antifungal and antiaflatoxin agents (Kaur et al., 2011).

With this regard, volatile compounds from Brussels sprouts (*Brassica oleracea* L. var. gemmifera DC.), cabbage (*Brassica oleracea* L.), kale (*Brassica oleracea* var. sabellica), radish (*Raphanus sativus* L.), and broccoli (*Brassica oleracea* L. var. botrytis L.) were extensively studied. Among them, the most important one is ally-l-isothiocyanate, a β-thioglycoside formed after the hydrolysis of glucosinolates by the enzyme myrosinase (Kumar et al., 2019). Hydrolysis occurs upon tissue damage, since glucosinolates are safely stored in the vacuole. Nitriles may be also produced as secondary products of the reaction. Thiocyanates and nitriles are hydrophilic compounds with high antioxidant capacity. They participate in plant defense systems as allelochemicals, volatile repellents, in the transcriptional regulation of the heat stress response, sulfur metabolism, water transport, stomatal opening, cell growth, and apoptosis (Bones et al., 2015). The isothiocyanate group (–N=C=S) is highly nucleophilic and able to bind thiols, amino groups of amino acids, peptides, and proteins. The antifungal and antiaflatoxin properties are mainly due to the inactivation of crucial enzymes, such as reductases, acetate kinases, and oxidases (Nazareth et al., 2016).

ANTIFUNGAL ACTIVITY OF BIOACTIVE COMPOUNDS

Natural plant extracts have been widely used since ancient times for their antimicrobial activity against insects, bacteria, and fungi (Bakkali et al., 2008). Many of them are already

employed as pharmaceuticals, feed and food additives, cosmetics and perfume ingredients because of their antioxidant capacity and strong organoleptic properties. Recently, their composition and biological activity have been investigated in relation to the antifungal activity and the ability to inhibit AF production by *Aspergillus* spp.

Carvacrol (Gómez et al., 2018), cinnamaldehyde (Bang et al., 2000; Xie et al., 2004; Tian et al., 2012b; Sun et al., 2016; Khorasani et al., 2017; Gómez et al., 2018), eugenol (Khorasani et al., 2017), limonene (Sharma and Tripathi, 2008; Rammanee and Hongpattarakere, 2011), p-cymene (Pinto et al., 2013), terpineol (Tian et al., 2012b; Kohiyama et al., 2015), thymol (Marei et al., 2012; Gorran et al., 2013; Kohiyama et al., 2015; Shen et al., 2016), and turmerone (Ferreira et al., 2013) are the main active compounds of cinnamon (*Cinnamomum verum* J. Presl), clove [*Syzygium aromaticum* (L.) Merr & L.M. Perry], lemon [*Citrus* × *limon* (L.) Burm. f.], oregano (*Origanum vulgare* L.), and thyme (*Thymus vulgaris* L.) extracts. Their structure is shown in **Figure 2**, and the main effects as antifungal agents in plant extracts or as pure compounds are presented in **Tables 1A** and **1B**, respectively.

Those compounds generally act synergistically and in a dose-dependent manner. The highest effects were registered using increasing amounts of bioactive compounds and the whole EOs instead of single compounds (Tian et al., 2012a; Ferreira et al., 2013; Pinto et al., 2013).

Plant extracts are very complex mixtures, and their composition varies according to plant species and chemotype, phenological stage, tissue, and method of extraction (Figueiredo et al., 2008). Accordingly, their effect often has multiple targets (**Figure 4**) and different modes of action (**Figure 5**). They induce cytotoxicity through multiple pathways: (i) disrupting cell membrane permeability and functionality; (ii) inhibiting enzymes involved in the synthesis of cell wall components; (iii) impairing ergosterol metabolism; (iv) inducing ultrastructural alterations in cell compartments leading to swelling, vacuolations, and cation leakage; (v) inhibiting cytoplasmic and mitochondrial enzymes; and (vi) altering the osmotic and the redox balance.

Effects on Cell Wall and Cell Membrane

Fungal cell wall is a dynamic component, essential to assure cell viability. Moreover, it is involved in multiple cell functions, including morphogenesis and pathogenesis. Chitin, glucans, and pectins are the major building blocks, and they are continuously remodeled to cope with cell growth and differentiation by enzymes, such as chitin and glucan synthases, glycohydrolases, and transglycosidases (Gow et al., 2017). Therefore, these enzymes are perfect physiological targets to inhibit fungal growth.

An extensive survey on the antifungal activity of 13 different commercially available monoterpenes was performed by Marei et al. (2012). Among all tested compounds, thymol, followed by limonene, had the highest inhibitory effect on cellulase and pectin methyl esterase enzymes of *Aspergillus niger*, *F. oxysporum*, and *Penicillium digitatum*. The rate of inhibition on *A. niger* was higher for the pectin methyl esterase (IC_{50} at 1.28 mg L^{-1}) rather than for the cellulase (IC_{50} at 44.56 mg L^{-1}). Cinnamaldehyde was found to be a non-competitive inhibitor of chitin synthase (IC_{50} at 111.0 mg L^{-1}) and *b*-(1,3)-glucan synthase (IC_{50} at 190.3 mg L^{-1}) (Bang et al., 2000).

Ergosterol is the main sterol derivative of fungi, and it is essential to preserve cell membrane functionality as cholesterol does in animal cells. In addition, it is essential to ensure the activity of membrane-bound enzymes. Owing to its essential role in fungal cells, many fungicides act by inhibiting its biosynthesis or binding it in the cell membrane (Sant et al., 2016). Phenols and aldehydes possess a sufficient hydrophobicity to pass the double phospholipid bilayer, to interact with ergosterol in the cell membrane, or to enter the nucleus and act as regulators for its biosynthesis. As a consequence, alteration of fatty acid profiles along with modification of cell membrane, osmotic imbalance leading to irreversible damage of the hyphae membranes, conidiophores, and death occur (Ansari et al., 2013).

Cinnamomum spp. EO or its main component, cinnamaldehyde, were reported to impair ergosterol biosynthesis at concentrations as low as 2 mg L^{-1} (Tian et al., 2012b) and to cause irreversible deleterious morphological and ultrastructural degenerative alterations of the fungal cell membrane at 104 mg L^{-1} (Sun et al., 2016; Khorasani et al., 2017). The same effect on fungal morphology was described for *Thymus vulgaris* L. (at 2,500 mg L^{-1}) (Kohiyama et al., 2015), *Curcuma longa* L. (Ferreira et al., 2013; Hu et al., 2014, 2017), and *Anethum graveolens* L. EOs (at 2 and 100 mg L^{-1} *in vitro* and in cherry tomatoes, respectively) (Tian et al., 2011).

Ergosterol biosynthesis may be regulated at the genomic level. Downregulation of ERG7, ERG11, ERG6, ERG3, and ERG5 genes by citral, the major component of lemongrass EO, was indeed reported for *P. digitatum* (OuYang et al., 2016).

Mitochondrial Dysfunction

Mitochondrial membrane potential is maintained in healthy cells by an electrochemical gradient through the electron transport chain, which is, ultimately, the major source of ATP molecules. As ATP levels decrease, the normal metabolic functions slow down until cell death occurs. The mechanism of action is not clearly understood. Several hypotheses have been made, including a direct inhibition of ATPases (see *Enzyme Inhibition*) and disruption of the osmotic balance, mainly causing calcium and protons leaking and, consequently, of the electrochemical potential. As for polygodial, a naturally occurring sesquiterpene dialdehyde isolated from different plant species, the mechanism was studied in depth, although with mammalian mitochondrial preparations. In this case, direct inhibition of enzymes was excluded. Indeed, the mechanism was supposed to rely on the uncoupling of the mitochondrial ATPase due to the modification of the electric properties of the membrane surface (Castelli et al., 2005). In yeasts, carvacrol was also responsible for the induction of calcium stress, mediated by the activation of specific intracellular signaling pathways (Rao et al., 2010).

TABLE 1A | Antifungal activity of plant extracts on *Aspergillus* spp.

Plant/compounds	Type of extract or oils	Major components	Antifungal activity	Concentration of active compound(s) (mg L^{-1} or ml L^{-1})	References
Jojoba oil		Gadoleic acid, erucic acid	Growth inhibition of *Aspergillus parasiticus*, *A. ochraceus*, *Fusarium solani*, *Penicillium* sp.	n.p.	Badr et al. (2017)
Jojoba pomace extract	Aqueous isopropyl extract, pH 4–5	84.7% phenols, 15.3% flavonoids			
Jatropha oil		Linoleic acid, oleic acid			
Jatropha pomace extract	Aqueous isopropyl extract, pH 4–5	78.4% phenols, 21.6% flavonoids			
Mentha (*Mentha pulegium L.)*	Aqueous extract	n.p.	Growth inhibition of *A. flavus*	8,000	Omidpanah et al. (2015)
Senna (*Cassia senna* L.)				6000	
Basil (*Ocimum basilicum* L.)				8,000	
Thyme (*Thymus vulgari*s L.)				2,000	
Safflower (*Carthamus tinctorius* L.)				4,000	
Hairy cistus (*Cistus incanus* L.)	Methanolic extract	n.p.	Growth inhibition of *A. parasiticus*; up to 90% of reduction of AFB_1 production in YES medium and 86% in macadamia nuts	n.p.	Kalli et al. (2018)
Cinnamon (*Cinnamomum zeglanicum* Garcin ex Blume)	Diluted water extract (3, 5, 7, and 9% *v/v*)	88.7% cinnamaldehyde	Up to 100% growth inhibition of *Aspergillus flavus* on PDA extract (using 3% extract after 1 day); 100% reduction of AFB_1 production in pistachio nuts	n.p.	Khorasani et al. (2017)
Clove (*Caryophyllus aromaticus* L.)		71.1% eugenol			
Thyme (*Thymus daenensis* Celak)		Thymol (73.9%) and carvacrol (6.7%)	Up to 100% growth inhibition of *Aspergillus flavus* on PDA extract (using 7% extract after 1 day); up to 100% reduction of AFB_1 production in pistachio nuts		
Oregano (*Origanum vulgare* L.)	Commercially available essential oil	86% carvacrol	Growth inhibition of *A. parasiticus and A. flavus* in maize extract medium under different environmental conditions (25–37°C, aw 0.99–0.96)	152–505	Gómez et al. (2018)
Cinnamon (*Cinnamomum verum* J. Presl)		66.5% cinnamaldehyde		295–675	

(Continued)

TABLE 1A | Continued

Plant/compounds	Type of extract or oils	Major components	Antifungal activity	Concentration of active compound(s) (mg L^{-1} or ml L^{-1})	References
Cinnamon *(Cinnamomum jensenianum* Hand.-Mazz.*)*	EO obtained by hydrodistillation	17.3% eucalyptol, 12.5% α-terpineol	Growth inhibition of *A. flavus, A. oryzae*, *A. niger*; up to 100% of reduction of AFB_1 production	2 (*in vitro*)–120 (*in vivo*)	Tian et al. (2012b)
Dill (*Anethum graveolens* L.)	EO obtained by hydrodistillation	n.p.	Growth inhibition of *A. flavus* by disruption of mitochondrial membrane potential (MMP), acidification of external medium, and mitochondrial ATPase and dehydrogenase activities	25–2,000	Tian et al. (2012a)
Dill (*Anethum graveolens* L.)	EO obtained by hydrodistillation	n.p.	100% growth inhibition of *Aspergillus* spp.	2	Tian et al. (2011)
			Up to 86.1 and 94.4% growth inhibition of *Aspergillus* spp. in healthy and wounded cherry tomatoes, respectively	100	
Thyme (*Thymus vulgaris* L.)	EO obtained by hydrodistillation	40.6% borneol, 19.9% α-terpineol, 12.3% camphene	Growth inhibition of *A. flavus*, up to 100% of reduction of AFB_1 production	1,500 (for AFB_1 reduction); 2,500 (for *A. flavus* growth inhibition)	Kohiyama et al. (2015)
Thyme (*Thymus daenensis* Celak)	Hydrodistillates resuspended in ethanol	n.p.	Mycelial growth and spore production inhibition of *A. flavus*, up to 100% of reduction of AFB_1 production	350	Gorran et al. (2013)
Savory (*Satureja khuzestanica*)					
Savory (*Satureja macrosiphonia* Bornm)			Mycelial growth and spore production inhibition of *A. flavus*, up to 56.8% of reduction of AFB_1 production	500	
Turmeric (*Curcuma longa* L.)	Hydrodistillates resuspended in 5% (*v/v*) Tween-20	Oxygenated sesquiterpenes (60.7%) Sesquiterpene hydrocarbons (34.3%)	Up to: 93.41% mycelial growth inhibition; 93.41% spore germination inhibition; 74.6% activity inhibition of mitochondrial ATPase and 84.7% dehydrogenases activity inhibition	n.p.	Hu et al. (2014)
Turmeric (*Curcuma longa* L.)	EO obtained by hydrodistillation	ar-turmerone (33.2%), α-turmerone (23.5%), ß-turmerone (22.7%)	Up to 99.0% inhibition of AFB_1 production using 5% (*w/w*) of extract	n.p.	Ferreira et al. (2013)
Ferula (*Ferulago capillaris Link ex Spreng.)*	EO obtained by hydrodistillation	α-Pinene (35.8%) and limonene (30.9%)	Inhibition of *Aspergillus* spp. growth	640–1,250	Pinto et al. (2013)

n.p., not provided.

TABLE 1B | Antifungal activity of pure commercial compounds on *Aspergillus* spp.

Plant/compounds	Antifungal activity	Concentration of active compound(s) (mg L^{-1} or ml L^{-1})	References
Isothiocyanate	Up to 100% of inhibition of *A. parasiticus* growth and aflatoxin production	0.01	Nazareth et al. (2016)
Isothiocyanate	Corn kernels	≥0.00005	Tracz et al. (2017)
Allyl isothiocyanate	Inhibition of *A. flavus* growth and aflatoxin production in corn, barley, and wheat in simulated silo system	0.0005	Quiles et al. (2015)
Allyl isothiocyanate	Inhibition of *Aspergillus parasiticus* growth and aflatoxin production in Brazil nuts	0.0000025	Lopes et al. (2018)
Curcumin	Up to 96.0% inhibition of AFB_1 production using 0.5% (*w/w*) of extract	n.p.	Ferreira et al. (2013)
Cinnamaldehyde	Inhibition of radial growth, spore, and aflatoxin production of *A. flavus*	104	Sun et al. (2016)
Camphene	Mycelial growth inhibition of *F. oxysporum, A niger, P. digitatum;* inhibition of pectin methyl esterase, cellulase, and polyphenol oxidase enzymes	From 121.5 to 314.2	Marei et al. (2012)
(R)-Camphor		From 157.1 to 367.0	
(R)-Carvone		From 432.5 to 120.0	
1,8-Cineole		From 36.4 to 148.4	
Cuminaldehyde		From 79.5 to 363.5	
(S)-Fenchone		From 193.8 to 330.6	
Geraniol		From 73.9 to 357.0	
Carbendazim		From 13.6 to 37.38	
(R)-Linalool		From 266.6 to 73.7	
(1R,2S,5R)-Menthol		From 121.9 to 394.4	
Myrcene		From 95.5 to 336.9	
Thymol		From 20.1 to 50.4	
(S)-Limonene		From 26.8 to 153.2	

n.p., not provided.

Enzyme Inhibition

Mitochondrial dysfunction may also occur via ATPase inhibition. Dill (*Anethum graveolens* L.) EO was shown to affect mitochondrial and plasma membrane ATPase at 0.08–0.64 ml L^{-1} (Pinto et al., 2013), while turmeric (*C. longa* L.) EO was shown to suppress mitochondrial dehydrogenases and mitochondrial ATPase at 2–8 ml L^{-1} (Hu et al., 2014). Turmeric EO was also found to exert antifungal activity via ATPase, malate dehydrogenase, and succinate dehydrogenase inhibition at 1–8 ml L^{-1} *in vitro* and 4 ml L^{-1} in maize (Hu et al., 2017). The reactivity of phenols and aldehydes in EOs to proteins and enzymes is the major mechanism, as reported for isothiocyanates.

Isothiocyanate were successfully used to inhibit *Aspergillus parasiticus in vitro* at doses of 5 mg (Manyes et al., 2015) or even in gaseous form in foods at concentrations of 100.01 ml L^{-1} in wheat flour (Nazareth et al., 2016), at ≥0.05 ml L^{-1} in corn kernels (Tracz et al., 2017), at 0.5 ml L^{-1} in corn, barley, and wheat in simulated silo system (Quiles et al., 2019), at 0.0025 ml L^{-1} in Brazil nuts (Lopes et al., 2018), and at 46,040 and 78,250 mg/kg in the Italian "piadina" (Saladino et al., 2016).

INHIBITORY EFFECT ON AFLATOXIN B_1 PRODUCTION

Aflatoxins are polyketide-derived furanocoumarins, the production of which depends upon 25 different genes, clustered together in a 70-kb DNA sequence region. The majority of the genes encodes for enzymes involved in the synthesis and participates as transcription factors, while others do not have a clear assigned function (Yu et al., 2004).

Many physiological events in fungal cells are regulated by oxidative bursts such as differentiation, switch from conidia to germ tube development, and the onset of secondary metabolism. In particular, oxidants are able to induce AF biosynthesis (Reverberi et al., 2006). In the presence of oxidative stress, the fungal antioxidant molecules (tocopherols, ascorbic acid, carotene, reduced glutathione) and enzymes (superoxide dismutase, catalase, and glutathione peroxidase) are induced concomitantly to AF biosynthetic gene cluster (Reverberi et al., 2010). Therefore, it was also suggested that AF production may also be a way to incorporate oxygen atoms and protect cells from oxidative damage (Kim et al., 2005). The mechanism of EOs or their components may be associated with their antioxidant activity, responsible for the attenuation of the fungal oxidative stress responses, thus AF production (Kim et al., 2005; Reverberi et al., 2005).

Different compounds have been proven to inhibit the production of secondary metabolites like AFB_1, at comparable or slightly lower concentrations than those that inhibit the mycelial growth, which is consistent with their supposed mode of action. The different inhibition pattern suggests that the suppressive effect is elicited

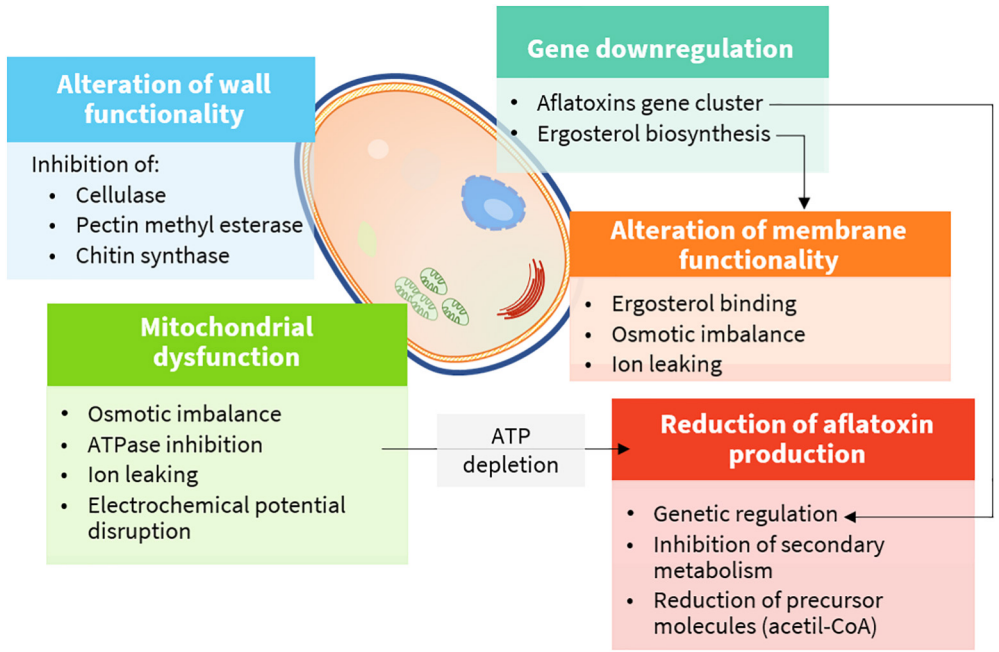

FIGURE 4 | Cellular targets and mechanisms of action of bioactive compounds (details are provided in the text).

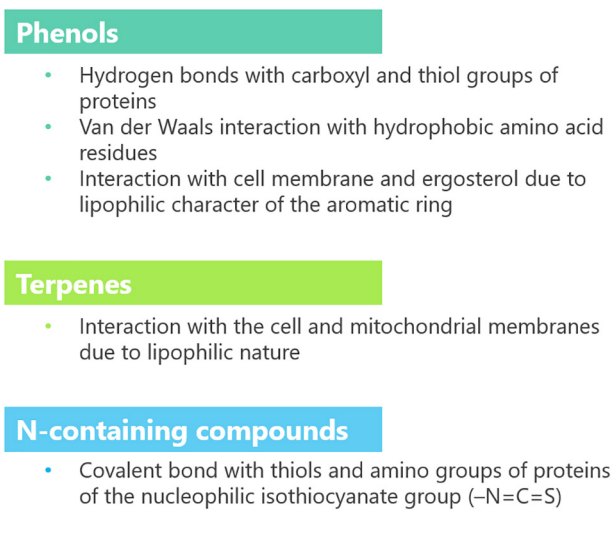

FIGURE 5 | Functional groups and mode of action of bioactive compounds.

on transcriptional regulators (AflR and AflS) as well as on structural genes (Georgianna and Payne, 2009), as reported in **Table 2**.

Eugenol was proved to be effective in downregulating aflM, aflD, aflC, aflP, aflR (Jahanshiri et al., 2015), aflP, aflM, aflD, and aflT (Liang et al., 2015; Lv et al., 2018) genes. Conversely, turmeric EO downregulated aflD, aflM, aflO, aflP, and aflQ genes (Hu et al., 2017). In a recent study by Moon et al. (2018) γ-terpinene was found to downregulate aflC, aflD, aflE, aflK, aflO, and aflQ genes, whereas citral downregulated aflD, aflE, aflK, aflL, aflO, aflQ, aflR, aflS, aflC, and aflG.

Finally, inhibition of the secondary metabolism as a consequence of the reduced fungal growth and ATP and AF precursor depletion (acetyl coenzyme A) by mitochondrial dysfunction may contribute to the general antiaflatoxigenic effect of these compounds (Tian et al., 2011).

AFLATOXIN DEGRADATION ACTIVITY

Various plant extracts were reported to degrade AFB_1 as well as other mycotoxins both *in vitro* and *in vivo*, as reported in **Table 3**.

In most of the studies, the active agents were water soluble, belonged to the flavonoids and phenol groups. Besides the activity of those low molecular weight compounds, the possible coextraction of enzymes able to degrade mycotoxins has to be taken into account. In fact, a detrimental effect on the degrading activity was observed after boiling, while no effect was registered after dialysis with 10–14 kDa cutoff membrane. This suggests that heat-sensitive, high-molecular weight compounds may play a significant role in AF degradation (Vijayanandraj et al., 2014; Ponzilacqua et al., 2019). Indeed, many enzymes, also belonging to plants, have been described for their ability to degrade AFs (Loi et al., 2017; Lyagin and Efremenko, 2019). Among them, polyphenol oxidases and laccases may also use low molecular weight compounds as redox mediators, thus enhancing their degradation capability through a synergistic or additive mechanism (Loi et al., 2018).

Although the mechanism of action is not clearly understood, some authors evaluated the outcome of the degradation

TABLE 2 | Aflatoxins genes regulated by bioactive compounds.

Gene	Function	Bioactive compound and references
aflC previously known as pksA	Polyketide synthase	Eugenol (Jahanshiri et al., 2015) γ-terpinene (Moon et al., 2018)
aflD previously known as nor-1	Reductase	Eugenol (Jahanshiri et al., 2015; Liang et al., 2015; Lv et al., 2018) Turmeric EO (Hu et al., 2017) γ-terpinene and citral (Moon et al., 2018)
aflE	Reductase	γ-Terpinene (Moon et al., 2018)
aflK	Versicolorin synthase	γ-Terpinene (Moon et al., 2018)
aflL	Desaturase	Citral (Moon et al., 2018)
aflM previously known as ver-1	Dehydrogenase/ ketoreductase	Eugenol (Jahanshiri et al., 2015; Liang et al., 2015; Lv et al., 2018) Turmeric EO (Hu et al., 2017)
aflO	Oxidoreductase/P450 monooxygenase	Turmeric EO (Hu et al., 2017) γ-Terpinene and citral (Moon et al., 2018)
aflP previously known as omtA	Methyltransferase	Eugenol (Jahanshiri et al., 2015; Liang et al., 2015; Lv et al., 2018) Turmeric EO (Hu et al., 2017)
aflQ	*O*-Methyltransferase	γ-Terpinene (Moon et al., 2018) Citral (Moon et al., 2018)
aflR	Transcriptional regulator	Eugenol (Jahanshiri et al., 2015 Citral (Moon et al., 2018)
aflS	Transcription enhancer	Citral (Moon et al., 2018)
aflT	Transmembrane protein	Eugenol (Liang et al., 2015; Lv et al., 2018)

by high-performance liquid chromatography (HPLC) and liquid chromatography tandem MS (LC-MS/MS). The chemical properties of AFs were deeply modified upon incubation with plant extracts. AFB_1 was modified in different ways, including the removal of the double bond of the furan ring and the modification of the lactone ring, resulting in a significant decrease in the cytotoxicity, evaluated on Hela cells (Velazhahan et al., 2010) and by Brine shrimps (*Artemia salina*) bioassay (Iram et al., 2015, 2016a,b). The toxic and carcinogenic potential of AFB_1 was indeed attributed to the difuran ring, which *in vivo* is quickly oxidized to 8,9-epoxy-AFB_1 and, to a lesser extent, to the lactone moiety (Loi et al., 2016).

DISCUSSION

The use of natural compounds in pre- and postharvest appears appealing, especially when compared to the use of antibiotics or fungicides from synthetic origin. Natural flavoring compounds derived from plants were listed as GRAS compounds in Europe and the United States: among others, clove, marjoram, thyme, nutmeg, basil, mustard, and cinnamon. However, despite their proven *in vitro* efficacy and their GRAS status, the use of those compounds as a pre- or postharvest treatment has different limitations: high volatility, poor stability due to oxidation reactions, and strong organoleptic features. This latter may lead to unpleasant tastes and off-flavors in food and feed or interfere with the signaling pathway mechanisms mediated by volatile compounds in the field. To overcome these limitations, different technologies have been studied to deliver bioactive components while preserving them from unwanted chemical reactions and controlling the organoleptic impact. Emulsification, spray drying, coaxial electrospray system, freeze drying, coacervation, *in situ* polymerization, extrusion, fluidized bed coating, and supercritical fluid technology are the most promising ones (Bakry et al., 2016). EOs can be also incorporated in edible coatings (Peretto et al., 2014; Alotaibi et al., 2019), films (Giteru et al., 2015), or even sprayed on food in a vapor form (Gao et al., 2014).

Among the different proposed technologies, the encapsulation of EOs has many advantages, i.e., even dispersion and release of EOs, odor masking, increased shelf life, and improved technological properties (easy dosing and pouring, increased solubility, dust-free material) (Wu et al., 2012; da Rosa et al., 2015).

The antifungal activity of encapsulated eugenol, menthol, and t-anethole (Kumar et al., 2019), *Illicium verum* Hook. f. (Dwivedy et al., 2018), *Cinnamomum zeylanicum* Garcin ex Blume (Kiran et al., 2016), and *Coriandrum sativum* L. (Das et al., 2019). EOs was investigated *in vitro* toward *A. flavus*, and was shown to reduce AFB_1 production with promising results. A recent study by Mateo et al. (2017) investigated the antiaflatoxigenic potential of a bioactive packaging based on ethylene-vinyl alcohol copolymer films incorporating EOs from *O. vulgare* L., *C. zeylanicum* Garcin ex Blume, or their major active constituents, carvacrol and cinnamaldehyde. On the contrary, the antifungal activity of allyl isothiocyanate was completely lost upon encapsulation (Janatova et al., 2015). This means that specific delivery systems have to be developed for each EO or bioactive compound.

Moreover, the effectiveness of the preharvest treatments also depends upon several biotic and abiotic factors. The treatment response may vary according to the specific plant species or cultivar, due to the activation of cultivar-specific defense pathways and different host–pathogen interaction patterns (Feliziani et al., 2015). Weather conditions and the phenological stage at the delivery may also affect the results of the treatment in the field.

Few *in vivo* trials were conducted to evaluate the efficacy of the use of natural compounds as antifungal agents, even though they focused on the reduction in the postharvest decay (Sivakumar and Bautista-Baños, 2014; Feliziani et al., 2015).

As regards the postharvest treatments, food matrix and composition, lipid content, water activity, pH, and enzymes can decrease their effectiveness as an antimicrobial or antifungal compound (Hyldgaard et al., 2012). Therefore, with respect to the *in vitro* studies, 1–3% higher amounts may be needed to achieve the same results (Firouzi et al., 2007). Nonetheless, when high amounts are used, the organoleptic properties of the food may be impaired. To overcome this issue, lower concentrations

TABLE 3 | Degradation activity of plant extract on aflatoxin B_1 (AFB_1).

Plant	Type of extract/oils	*In vitro*/*in matrix* AFB_1 reduction	Relative toxicity of AFB_1 degradation products	References
Araçá (*Psidium cattleianum*)	Aqueous extract	Up to 30% of AFB_1 degradation (16.67 μg/L) after 48 h of incubation in aqueous medium, pH 6.0–7.0	n.p.	Ponzilacqua et al. (2019)
Rosemary (*Rosmarinus officinalis* L.)		Up to 60% of AFB_1 degradation (16.67 μg/L) after 48 h of incubation in aqueous medium, pH 6.0–7.0	n.p.	
Oregano (*Origanum vulgare* L.)		Up to 38% of AFB_1 degradation (16.67 μg/L) after 48 h of incubation in aqueous medium, pH 6.0–7.0	n.p.	
Basil (*Ocimum basilicum* L.)	Aqueous extract	Up to 90% of AFB_1 degradation (100 μg/L) after 72 h at 60°C in aqueous extract;	70% of mortality reduction by Brine shrimps (*Artemia salina*) bioassay	Iram et al. (2016a)
		In matrix degradation (maize) up to 90.4% of degradation after 72 h of incubation at 30°C, pH 8		
Golden tree *(Cassia fistula* L.*)*		Up to 54% of AFB_1 degradation (100 μg/L) after 72 h at 60°C in aqueous extract;	n.p.	
		Up to 62.5% of AFB_1 degradation (100 μg/L, spiked) in maize after 72 h of incubation at 30°C, pH 8		
Ajowan caraway (*Trachyspermum ammi* L.) Sprague ex Turrill	Aqueous extract	Up to 92.8% of AFB_1 degradation (100 μg/L) after 72 h of incubation at 30°C, pH 8	72% of mortality reduction by Brine shrimps (*Artemia salina*) bioassay	Iram et al. (2016b)
		Up to 89.6% of AFB_1 degradation (100 μg/L, spiked) in maize after 72 h of incubation at 30°C, pH 8		
Lemon Scented Eucalyptus (*Corymbia citriodora*)	Leaf aqueous extract	Up to 95.21% of AFB_1 degradation (100 μg/L) after 72 h of incubation at 30°C, pH 8;	75% of mortality reduction by Brine shrimps (*Artemia salina*) bioassay	Iram et al. (2015)
		Up to 70.26% of AFB_1 degradation (100 μg/L, spiked) in maize after 72 h of incubation at 30°C, pH 8		
Garlic (*Allium sativum* L.)	Aqueous extracts	61.7% of AFB_1 degradation (50 μg/L) after 1 h of incubation at 37°C in PBS medium; 68.3% after 1 h of incubation at 37°C in real-contaminated sample using 50 mg/L of extract	n.p.	Negera and Washe (2019)
Lemon (*Citrus limon* L.)		56.0% of AFB_1 degradation (50 μg/g, spiked) after 1 h of incubation at 37°C in PBS medium; 60.6% after 1 h of incubation at 37°C in real-contaminated sample using 50 mg/L of extract		
Thyme (*Thymus daenensis* Celak)	Hydro-distillates	Up to 97% of AFB_1 degradation (2,000 μg/L) using 2,000 mg/L aqueous extract	n.p.	Gorran et al. (2013)
Savory (Satureja khuzestanica)		Up to 5% of AFB_1 degradation (2,000 μg/L) using 2,000 mg/L aqueous extract		
Savory (*Satureja macrosiphonia* Bornm)		Up to 13% of AFB_1 degradation (2,000 μg/L) using 2,000 mg/L aqueous extract		
Ajowan (*Trachyspermum ammi* L.) Sprague ex Turrill	Seeds aqueous extract	Up to 61% of AFB_1 degradation after incubation at 38°C for 48 h	No chromosomal aberrations induced in corn	Velazhahan et al. (2010)
Basil (*Ocimum tenuiflorum* L.)	Leaves aqueous extract	Up to 74.7% of AFB_1 degradation after incubation at 85°C for 4 h;	73.7% of cytotoxicity reduction on Hela cells	Panda and Mehta (2013)
		Up to 70.2% of AFB_1 degradation (1 μg/g, spiked) in rice after 4 h of incubation at 85°C		

n.p., not provided.

with bacteriostatic or fungistatic effects can be used, or they can be applied in combination with other antimicrobial compounds in a "multiple-hurdle approach" (Prakash et al., 2015; Sudharsan et al., 2019). Few authors evaluated the application in food to reduce AFB_1 contamination, mainly nuts like macadamia (Kalli et al., 2018) and pistachio (Khorasani et al., 2017), obtaining comparable results with respect to the *in vitro* analyses.

Feed Applications

Bioactive compounds are used in feed to enhance (i) the organoleptic characteristics of feed (as feed flavorings), (ii) feed stability (as antioxidants), and (iii) feed digestibility and gut flora stability (as zootechnical additives) [Regulation (EC) No 1831/2003, 2003].

The European Commission approved the use of linalool, thymol, eugenol, carvone, cinnamaldehyde, vanillin, carvacrol, citral, and limonene as flavorings in food products with no restriction. A stepwise approach was adopted to evaluate the safety of those compounds, including the evaluation of the structure–activity relationships, intake from current uses, toxicological threshold of concern, and available data on metabolism and toxicity [Commission Implementing Regulation (EU) No 872/2012, 2012].

Simple and substituted phenols like thymol and carvacrol, have been proposed so far as flavoring additives in feed for all animal species; thus, the demonstration of efficacy was not considered necessary for their approval by the European Food Safety Authority [EFSA], 2012. Thanks to their antioxidant capacity, these compounds enhance the stability, the quality, the palatability of animal feed, and prolong the shelf life.

The so-called "phytogenic" feed additives (PFAs) are simple or complex mixtures of compounds belonging to a wide variety of herbs, spices, EO, or non-volatile extracts, which can be used in feed for various purposes. PFAs can be applied as solid powders, granulated, or also in liquid form to premixtures or complete feeds (Steiner and Syed, 2015).

Bioactive compounds are widely used as zootechnical additives to increase animals weight gain and performance. A general positive effect was shown for feed intake, weight gain, and feed conversion rate in piglets, sows, and poultry, while inconsistent data were registered for apparent digestibility in piglets (Franz et al., 2010; Christaki et al., 2012; Zeng et al., 2015) possibly due to improved secretion of digestive enzymes and bile secretion (Hafeez et al., 2015). A positive effect on gut microbiota in monogastric animals was also reported by several authors (Tiihonen et al., 2010; Bento et al., 2013). On the contrary, there is still no evidence of the *in vivo* efficacy on ruminants, while discordant data are available from *in vitro* studies with ruminal models. EOs may improve nitrogen uptake and energy production but at the same time be toxic for the ruminal microbiota, which produces volatile fatty acid and inhibits ruminal methanogenesis (Giannenas et al., 2013).

Two feed additives made of a mixture of encapsulated EOs (carvacrol, methyl salicylate and L-menthol, thymol, D-carvone) from oregano (*O. vulgare* L.) and from caraway seed (*Carum carvi* L.) were positively evaluated by EFSA as growth enhancers for weaned piglets, chickens for fattening, chickens reared for laying, and minor avian species to the point of lay (European Food Safety Authority [EFSA], 2019a,b).

Despite the different uses in animal nutrition, the use as AF-reducing agents in feed is still unexplored. To be used as a feed additive to reduce AF contamination, EOs shall undergo a scientific assessment by EFSA to assure that several requirements are met: (i) the chemical compound is fully characterized and safe to be used; (ii) it leads to an irreversible and effective detoxification; (iii) the products of the detoxification process are not harmful or are less harmful than the contaminant itself to animals, people, or the environment; and (iv) the chemical and organoleptic characteristics of the feed are not altered (Commission Regulation (EU) 2015/786, 2015). A clear gap of knowledge for the identification of the degradation products and the evaluation of their toxicity currently limits this application.

In vivo studies often show low reliability because the EO composition is usually not fully characterized and active compounds quantified; the effects are not clearly defined because there may be differences in gastrointestinal tract anatomy and functionality also within the same species. When the studies are commercially oriented, some information may be voluntarily scarce (Stevanović et al., 2018). Eventually, limited information is available regarding the interaction between EOs and feed ingredients or other feed additives, such as fibers, probiotics, vitamins, and organic acids (Zeng et al., 2015).

CONCLUSION AND FUTURE PERSPECTIVES

Bioactive compounds from plant species are recognized for their pharmacological and nutraceutical value and are endowed with antifungal and antiaflatoxin activities.

The application of natural compounds deriving from plants to control aflatoxigenic fungi and AF production has been explored mostly *in vitro* in the last 10 years. The mechanisms of action are diverse and mainly target the cell wall, the plasmatic membrane, proteins, and the mitochondrial functionality of fungal cells. Some compounds also act as downregulators of AF biosynthetic pathway, while others have a direct degrading activity toward AF molecules. Limited studies evaluate the applicability of such compounds in food and feed to reduce *Aspergillus* spp. and AFs contamination. Nonetheless, many compounds possess the GRAS status and can be used as food and feed additives in Europe. Bioactive compounds are used as flavoring, antioxidant, and zootechnical additives to improve weight gain and digestibility of feeds in non-ruminant species. Exploring new technologies to extract and use antifungal compounds from food wastes, such as olive oil wastewater or winery by-products, or to deliver such compounds can increase sustainability and lower the cost of these compounds.

Enriching and expanding the genetic repertoire of plant secondary metabolites could help in increasing the plant defense systems. The identification of biosynthetic pathways, plant–host interactions, and varieties with higher content of bioactive compounds are crucial to allow the production of molecules of high commercial value and to improve the safety and quality of plant products. Another possible strategy to counteract AF contamination may be to increase the production of bioactive compound in susceptible commodities.

The major challenges that have to be overcome are the characterization of the active(s) compounds, the standardization of doses and biological activity, the evaluation of interactions in the field or with the food/feed matrix, the identification and the toxicological characterization of the degradation products in the case of the application to AF-contaminated commodities. Nonetheless, the potentialities of these compounds are diverse and may represent a powerful to counteract *Aspergillus* spp. contamination and AF production both in pre- and postharvest.

AUTHOR CONTRIBUTIONS

ML and CP wrote the manuscript. AL conceived the review. GM coordinated the contributions. All authors contributed to manuscript revision, read and approved the submitted version.

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