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## **Phenolamides: Plant specialized metabolites with a wide range of promising pharmacological and health-promoting interests**

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### **Abstract**

Phenolamides constitute a family of metabolites, widely represented in the plant kingdom, that can be found in all plant organs with a predominance in flowers and pollen grains. They represent a large and structurally diverse family, resulting from the association of phenolic acids with aliphatic or aromatic amines. Initially revealed as active compounds in several medicinal plant extracts, phenolamides have been extensively studied for their health-promoting and pharmacological properties. Indeed, phenolamides have been shown to exhibit antioxidant, anti-inflammatory, anti-cancer and antimicrobial properties, but also

protective effects against metabolic syndrome and neurodegenerative diseases. The purpose of this review is to summarise this large body of literature, including *in vitro* and *in vivo* studies, by describing the diversity of their biological properties and our actual knowledge of the molecular mechanisms behind them. With regard to their considerable pharmacological interest, the question of industrial production is also tackled through chemical and biological syntheses in engineered microorganisms. The diversity of biological activities already described, together with the active discovery of the broad structural diversity of this metabolite family, make phenolamides a promising source of new active compounds on which future studies should be focused.

Keywords: phenolamides, kukoamine, putrescine, tyramine, clovamide, avenanthramide, human health

## 1. Introduction

Phenolamides, also known as hydroxycinnamic acid amines (HCAA) or phenylamides, are plant specialized metabolites widely distributed in the plant kingdom (Martin-Tanguy et al., 1978; Herrmann and Nagel, 1989; Bienz et al., 2005; Bassard et al., 2010). The phenolamide structure is characterised by the association of at least one hydroxycinnamic acid derivative which is linked through an amide bond to an aromatic monoamine or an aliphatic polyamine (Fig. 1). In nature, the most common hydroxycinnamic acid derivatives are *p*-coumaric, ferulic, caffeic and sinapic acids, together with some glycosylated forms. Regarding the amine moieties, the aromatic monoamines are either phenolic (dopamine, octopamine, tyramine, noradrenaline, anthranilic acid) or indolic (serotonin, tryptamine) whereas the aliphatic polyamines differ in C length and N number (agmatine, putrescine, cadaverine, spermidine and spermine) (Fig. 1).

The combination of different hydroxycinnamic acid and amine moieties together with the possibility of one to four N-substitutions on aliphatic polyamines are responsible for the broad structural diversity for phenolamides. In a recent study, Li and coworkers constructed an *in silico* phenolamide database containing more than 840 possible structures based only on the most common hydroxycinnamic acid and amine moieties (Li et al., 2018b). Even if all these structures have not been detected in nature, the recent development of specific Liquid Chromatography High Resolution Mass Spectrometry (LC-HRMS) methods has allowed for the detection of at least 79 different phenolamides from different organs in only four different plants (corn, wheat, rice and tobacco) (Li et al., 2015, 2018b).

The phenolamide distribution within plants is well-documented (Martin-Tanguy et al., 1978; Luo et al., 2009; Bassard et al., 2010; Kaur et al., 2010; Dong et al., 2015). They can be found

in all plant organs and sometimes at high concentrations, especially at the surface of pollen grains and seeds (Luo et al., 2009; Grienenberger et al., 2009; Vogt, 2018; Delporte et al., 2018) or in wounded tissues (Roepenack-Lahaye et al., 2003a; Zacarés et al., 2007; Kaur et al., 2010; Onkokesung et al., 2012). Contrary to the knowledge on their occurrence and distribution, their physiological roles are still poorly understood. Roles in plant defence against pathogens and herbivores have been suggested and sometimes demonstrated (Zacarés et al., 2007; Kaur et al., 2010; López-Gresa et al., 2010; Alamgir et al., 2016). However, no clear function is associated to their presence in large amounts in floral organs and pollen (Fellenberg et al., 2009; Vogt, 2018).

The bioactivity of phenolamides was initially investigated in the 1970s, and nowadays is mostly done in an ethnopharmacological context. Indeed, Asian medicinal herbs and berries, such as goji berries (wolfberries, fruits of *Lycium barbarum* L.), jikoppi (root bark from *Lycium chinense* Miller), shoo-fly herb (apple-of-Peru, *Nicandra physaloides* Schreb.), safflower (*Carthamus tinctorius* L.), Maltese cross (fruits of *Tribulus terrestris* L.), veloutier (*Heliotropium foertherianum* Diane & Hilger) and shān làng dàng (*Scopolia tangutica* Maxim.), which exhibit a plethora of properties beneficial to health, are rich in various phenolamides that have been screened and often revealed as active principles (Funayama et al., 1980; Koyama et al., 2006; Long et al., 2014). A recent review on *Lycium* genus phytochemistry reported 42 different phenolamides, representing about 12% of the known metabolites in this genus (Qian et al., 2017). Since then, this list has become longer (Zhu et al., 2017; Xia et al., 2019; Zhu et al., 2020). In addition, the occurrence of phenolamides in edible vegetables such as eggplant (*Solanum melongena* L.), tomato (*Solanum lycopersicum* L.), cocoa (*Theobroma cacao* L.), oat (*Avena sativa* L.) and others has allowed us to consider them as potential health-promoting food ingredients. The range of health-related biological

properties of phenolamides is wide. They include anti-inflammatory, antioxidant, antimicrobial and anti-cancer properties together with activities protecting humans from metabolic syndrome, cardiovascular diseases and neurodegenerative diseases. The objective of this review is to present the current state of art regarding the health-promoting and pharmacological properties of phenolamides with the molecular mechanisms supporting them. In addition, from the perspective of more intensive usage in the future, a section of this review will be devoted to their chemical and biological production in microorganisms.

## 2. Protective activities against metabolic syndrome

The metabolic syndrome groups a cluster of metabolic disturbances such as glucose intolerance, insulin resistance, dyslipidaemia and hypertension, which all constitute risk factors for atherosclerotic cardiovascular diseases, stroke and diabetes (Eckel et al., 2005; Mottillo et al., 2010). The emergence of metabolic syndrome is linked to an increase in obesity worldwide, associated with a high-fat/high-glucose diet (Moreno-Fernández et al., 2018). Indeed, expanded adipose tissue appears as the major contributor to metabolic syndrome development by (i) increasing blood levels of fatty acids, which also contributes to hyperinsulinemia due to reduced insulin sensitivity in muscles and increased insulin export from the pancreas and (ii) inducing a pro-inflammatory state, through the increased expression of two pro-inflammatory cytokines, interleukin (IL)-6 and Tumor Necrosis Factor  $\alpha$  (TNF $\alpha$ ), which counteract the anti-inflammatory effect of the insulin-sensitising cytokine adiponectin. Increasing blood adiponectin levels is therefore a target to prevent metabolic syndrome. *In vitro*, the synthetic phenolamide *N*-(2-phenylethyl)ferulamide exhibits adiponectin inducing activity comparable to the reference drug pioglitazone in mouse 3T3-L1 cells and human pre-adipocytes (Yamazaki et al., 2008). This inducing effect is linked to the

transcriptional activation of the Peroxisome Proliferator-Activated Receptor  $\gamma$  (PPAR $\gamma$ ) Retinoid X receptor  $\alpha$  (RXR $\alpha$ ) heterodimer. Bioassays on diabetic male KK-A $\gamma$ /Ta mice concluded that a diet containing 1% *N*-(2-phenylethyl)ferulamamide significantly reduces blood glucose and triglyceride blood levels after 5 weeks (Yamazaki et al., 2008).

Controlling the blood glucose level is another alternative to prevent metabolic syndrome.  $\alpha$ -glucosidase is involved in glycogen and starch hydrolysis to glucose. Among the phenolamides, *p*-coumaroyltyramine, *p*-coumaroylputrescine, feruloylputrescine and diferuloylputrescine have exhibited inhibitory activity against yeast  $\alpha$ -glucosidase (Nishioka et al., 1997; Niwa et al., 2003; Song et al., 2016). In particular, *p*-coumaroyltyramine showed very high efficiency with a  $K_i < 1 \mu\text{M}$  and important specificity for  $\alpha$ -glucosidase, since  $\beta$ -glucosidase,  $\alpha$ -amylase,  $\alpha$ -galactosidase and  $\alpha$ -mannosidase were not inhibited (Niwa et al., 2003; Song et al., 2016). Molecular docking analyses of *p*-coumaroyltyramine on a homology model structure of  $\alpha$ -glucosidase indicated that it was positioned at the entrance of the active site and highlighted the importance of the phenolic acid moiety, specifically the hydroxyl group on the phenolic cycle and the double bond between the phenolic cycle and the amine group for the stabilisation of the inhibitor (Song et al., 2016). Kukoamine B ( $\text{N}^1, \text{N}^{10}$ -bis(dihydrocaffeoyl)-spermine) was recently shown to lower blood glucose in a type 2 diabetic mouse model (db/db) (Li et al., 2019). This effect on blood glucose was accompanied by a decrease in triglycerides, cholesterol and phosphatidylethanolamide, together with a reduction in several pro-inflammatory cytokines, making kukoamine B a potential candidate drug for the treatment of type 2 diabetes mellitus (Li et al., 2019).

Atherosclerosis constitutes one of the major outcome risks of metabolic syndrome (Cornier et al., 2008; Tsai et al., 2018). Atherosclerosis is an inflammatory process affecting the vessel

walls of arteries, which can ultimately lead to cardiovascular diseases. This complex process is well-explained and described in a review by Galkina and Ley (2009). Feruloylserotonin and *p*-coumaroylserotonin were identified as the active components in safflower extract that exhibited anti-atherosclerotic properties. Indeed, supplementation of the diet with safflower (*Carthamus tinctorius* L.) extracts or serotonin derivatives to mice deficient in apolipoprotein E (a mouse model of atherosclerosis) reduced the atherosclerotic lesion area (Koyama et al., 2006). Since this effect was accompanied by a reduction in the plasma lipid peroxide level, it was concluded that *p*-coumaroylserotonin and feruloylserotonin may attenuate atherosclerotic lesion development through the oxidative protection of lipids. This study was confirmed on Kurosawa and Kusanagi-Hypercholesterolemic rabbits, in which long-term dietary supplementation led to a decrease in atherosclerotic lesions and higher vascular distensibility (Katsuda et al., 2009). In addition, diet supplementation with safflower extract for 4 weeks in a small number of human volunteers led to a reduction in the plasma level of oxidised LDL, which was associated with a reduction in some cardiovascular risk markers (Koyama et al., 2008).

The mechanisms of action of safflower serotonin derivatives to limit atherosclerotic lesion formation appear to be numerous. Indeed, Piga and collaborators have shown that *p*-coumaroylserotonin and feruloylserotonin inhibit *in vitro* adhesion and migration of the U-937 human monocyte cell line toward human endothelial aortic cells (HEAC), which are key steps in the early development of atherosclerotic lesions. This inhibition appeared to be linked to the antioxidant properties of these phenolamides, which interrupted the Reactive Oxygen Species (ROS)-dependent induction of Vascular Adhesion Molecule 1 (VCAM-1), an adhesion factor for leukocytes, and that of Monocyte Chemoattractant Protein 1 (MCP-1), a chemoattractant of monocytes synthesised by HEAC (Piga et al., 2009). Another study



indicated that *p*-coumaroylserotonin and feruloylserotonin inhibited, in a concentration-dependent manner, the phenylephrine-induced vasoconstriction state on rat femoral artery rings. They also inhibited the proliferation and migration of vascular smooth muscle cells (VSMCs) by blocking the Platelet Derived Growth Factor (PDGF) signalling cascade or the intracellular  $[Ca^{2+}]$  increase (Takimoto et al., 2011). Interestingly, the oat-specific phenolamide, avenanthramides (Avns) also inhibited U-937 monocyte cell line adhesion to HEAC and decreased VCAM-1 and MCP-1 expression, as well as the expression of IntraCellular Adhesion Molecule-1 (ICAM-1) (Liu et al., 2004).

Platelet aggregation plays an important role in the mechanism of atherosclerotic plaque formation inside the artery. Among other phenolamides, feruloyltyramine, caffeoyldopamine and hydroxybenzoyltyramine derivatives are able to inhibit platelet aggregation in the mouse. This effect is mediated by the inhibition of cyclooxygenase activity and a decrease in cAMP accumulation, which initiate the platelet aggregation cascade through P-selectin activation (Park, 2009, 2015, 2016).

### 3. Vascular system

In addition to atherosclerosis, phenolamides appear to be beneficial molecules in other aspects of cardiovascular system disease. Indeed, the hypotensive property of the oriental medicine plant jikoppi has been attributed to  $N^1, N^{14}$ -bis(dihydrocaffeoyl)-spermine, also called kukoamine A (Funayama et al., 1980). This initial study did not determine the mechanisms underlying this property. However, a more recent study, devoted to identifying the bitter-active compounds of the tropical fruit lulo (*Solanum quitoense* L., Solanaceae), isolated two spermidine containing phenolamides, i.e. ( $N^1, N^4, N^8$ -tris(dihydrocaffeoyl)-spermidine and  $N^1, N^8$ -bis(dihydrocaffeoyl)-spermidine), with a structure very close to that of

kukoamine A. Interestingly, the former metabolite exhibited strong inhibitory activity against Angiotensin-Converting Enzyme (ACE), a carboxypeptidase that plays an essential role in blood pressure regulation (Dorer et al., 1974). Docking analysis of N<sup>1</sup>,N<sup>4</sup>,N<sup>8</sup>-tris(dihydrocaffeoyl)-spermidine and N<sup>1</sup>,N<sup>8</sup>-bis(dihydrocaffeoyl)-spermidine in the active site of ACE highlighted a strong protein-inhibitor interaction in both cases, mediated by a hydrophobic interaction through the aromatic ring and hydrogen bonds through the dihydrocaffeoyl moieties (Forero et al., 2016). Due to the structural homology of kukoamine A with these metabolites, it is reasonable to hypothesise that its hypotensive activity could be mediated by a similar mechanism.

Clovamide (N-caffeoyl-dihydroxyphenylalanine) is a phenolamide initially isolated from red clover (*Trifolium pratense* L.) (Yoshihara et al., 1974), largely present in the *Trifolium* genus and in cocoa (*Theobroma cacao* L.). This phenolamide exhibited a protective effect against oxidative stress on the rat cardioblast cell line H9c2. It acts by limiting the ROS content in H<sub>2</sub>O<sub>2</sub> treated H9c2 cells, also by decreasing apoptosis events, such as DNA fragmentation and caspase activation (Zamperone et al., 2014). This antioxidant effect on cardioblast cells is interesting since myocardial damage after heart attack and/or stroke is usually caused by sequential ischemia/reperfusion, which promotes oxidative stress (Chiong et al., 2011). Clovamide has also been demonstrated to limit oxidative stress-induced damage to blood platelets and plasma (Kolodziejczyk et al., 2011).

#### 4. Anti-inflammatory properties

Inflammation is a complex process involved in the immune response of an organism to various stimuli such as infection and/or tissue injury (Medzhitov, 2008). This process is temporally and spatially controlled by plasma and cellular regulators and is viewed as a lever

to maintain the basal homeostatic state. The modern lifestyle, through different stressors such as a high-fat and/or high-glucose diet, constantly impacts on basal homeostasis, and may induce a chronic inflammatory state (Medzhitov, 2008; Kotas and Medzhitov, 2015). Chronic inflammation is a risk factor and a contributor to a large array of chronic diseases, including type 2 diabetes (Donath and Shoelson, 2011), cardiovascular diseases (Taube et al., 2012), cancers (Lu et al., 2006; Trinchieri, 2012) and neurodegenerative diseases (Hirsch and Hunot, 2009). Identifying and characterising efficient, possibly natural-source anti-inflammatory molecules is thus of major concern. Numerous phenolic compounds are efficient anti-inflammatory molecules (Yahfoufi et al., 2018). Several studies have evaluated the anti-inflammatory properties of phenolamides, as part of active principle from natural sources (food, herbal medicine) or as chemically synthesised compounds. Due to the complexity of inflammatory processes, multiple targets and markers for anti-inflammatory properties have been studied, and inter-molecule and inter-study comparisons are often difficult. For the ease of the reader, the anti-inflammatory properties of phenolamides are summarised in Fig. 2.

A classical model to study potential anti-inflammatory properties of molecules is to stimulate monocytes and/or macrophages with pro-inflammatory molecules such as lipopolysaccharide (LPS) and verify if the added molecule(s) is able to counteract this effect. For example, using the murine RAW 267.4 cell line stimulated with LPS, several phenolamides including tyramine, dopamine, tryptamine, spermidine, anthranilic acid and phenethylamine derivatives have been screened and demonstrated to inhibit the production of nitric oxide (NO) with  $IC_{50}$  values ranging from 2 to 50  $\mu$ M (Kim et al., 2012; Jiang et al., 2015; Wang et al., 2017b; Kim et al., 2018a; Wang et al., 2018; Hu et al., 2019; Wang et al., 2020). The mechanisms involved have been deciphered in the case of

dihydrocaffeoyltyramine, feruloyltyramine, *p*-coumaroyldopamine, dicoumaroylputrescine, diferuloylputrescine, avenanthramides (Avns) and clovamide (Fig. 2). Dicoumaroylputrescine, diferuloylputrescine and *p*-coumaroyldopamine were shown to inhibit the nuclear translocation of the transcription factor NFκB, which stimulates the transcription of numerous genes such as the pro-inflammatory cytokines IL-1, IL-6 and TNFα (Kim et al., 2012; Lee et al., 2015). Dihydrocaffeoyltyramine and feruloyltyramine inhibit prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) synthesis by controlling cyclooxygenase 2 (COX-2) expression. Both tyramine derivatives inhibit transcription factor activating protein 1 (AP1) and CCAAT/enhancer-binding protein (C/EBPβ) nuclear translocation by blocking c-Jun N-terminal kinase (JNK) and extracellular signal-regulated kinase (ERK) phosphorylating activity (Han et al., 2010; Jiang et al., 2015; Wang et al., 2020). The anti-inflammatory activity of tyramine derivatives (dihydrocaffeoyl- and caffeoyl) has been confirmed in other cell types, such as the human embryonic kidney cell line (HEK-293). Again, this activity was mediated by the inhibition of NFκB nuclear translocation (Xie et al., 2014). Interestingly, these two phenolamides exhibited contrasted anti-inflammatory efficiencies, indicating that the C7-C8 double bond of the phenolic moiety (the only difference between the two molecules) was important for this activity. In a skeletal muscle cell line (C2C12), Avns inhibited TNFα-induced inflammation through a reduction in NFκB translocation, the downregulation in IL-1 and IL-6 expression and impaired ROS accumulation (Yeo et al., 2019; Kang et al., 2018b). Interestingly, molecular docking studies revealed that Avns (A, B and C) inhibit the NFκB pathway through an allosteric inhibition of IκB kinase b (IKKβ) (Kang et al., 2018a, 2018b).

Another phenolamide, clovamide, has been studied on human monocytes pretreated with phorbol 12-myristate 13-acetate (PMA) and has shown a strong anti-inflammatory activity.

Clovamide inhibits superoxide anion production and TNF $\alpha$  and IL-6 synthesis. This inhibition appears again to be mediated by the inhibition of NF $\kappa$ B nuclear translocation (Zeng et al., 2011).

Oatmeal has long been used to treat itch associated with diverse xerotic dermatitis (Kurtz and Wallo, 2007). Avenanthramides appear to be associated at least partly with this property, since they exhibit anti-inflammatory activity on dermal fibroblasts, keratinocytes and mast cells (Inoue et al., 1997; Sur et al., 2008; Lotts et al., 2017; Dhakal et al., 2019). Purified Avns limit TNF $\alpha$ -induced keratinocyte inflammation by reducing the expression of NF $\kappa$ B and the release of IL-8 (Sur et al., 2008). The synthetic Avn Tranilast reduces dermal fibroblast inflammation by decreasing the expression of COX-2, which negatively impacts PGE<sub>2</sub> production (Inoue et al., 1997; Darakhshan and Pour, 2015). Interestingly, the topical application of purified Avns reduces both neurogenic inflammation and the immune-mediated allergic response in a murine itch model (Sur et al., 2008).

## 5. Neuroprotective properties

Neurodegeneration is the basis of numerous pathologies, including ischemic stroke and neurodegenerative diseases (Parkinson's disease, Alzheimer's disease, multiple sclerosis, etc.). Neurodegeneration is a complex process that can be induced notably by oxidative and inflammatory stresses (Chen et al., 2011, 2016; Singh and Devasahayam, 2020). The anti-inflammatory properties of clovamide and its derivatives were confirmed *in vitro* using specific cellular models of neuro-inflammation such as LPS treated BV-2 cells or SH-SY5Y cells (Fallarini et al., 2009; Lim et al., 2015; Hu et al., 2018). Clovamide synthetic derivatives appeared to efficiently inhibit NO production in inflammation-induced cells. This was the consequence of multistep impact on the induced inflammation pathway (Fig. 2) which

included the inhibition of JNK, extracellular signal-regulated kinase-mitogen activated protein kinase (ERK-MAPK) and I $\kappa$ B phosphorylation (Lim et al., 2015), as well as the inhibition of NF $\kappa$ B nuclear translocation (Lim et al., 2015; Hu et al., 2018), as well as the inhibition of IL-1, IL-6, TNF $\alpha$ , inducible nitric oxide synthase (iNOS) and COX-2 expression (Lim et al., 2015; Park et al., 2017; Hu et al., 2018). Finally, direct inhibition of the iNOS activity has been demonstrated for some clovamide derivatives, supported by molecular docking evidence for the active site of iNOS (Hu et al., 2018).

A larger panel of phenolamide structures including clovamide derivatives, kukoamine A, tyramine and octopamine derivatives have been studied for their neuroprotective properties using *in vitro* H<sub>2</sub>O<sub>2</sub>-induced and neurotoxin-induced cell models (Hu et al., 2015; Wang et al., 2017a; Hu et al., 2017; Feng et al., 2019). Indeed, kukoamine A and the clovamide derivative caffeoylphenylalanine methyl ester reduced ROS production in H<sub>2</sub>O<sub>2</sub>-induced SH-SY5Y cells. In addition, they inhibited the induction of apoptosis by reducing mitochondrial membrane potential (MMP) loss, modulating the level of malondialdehyde (MDA) and affecting the level of apoptotic markers such as the Bax/Bcl2 ratio and cleaved caspase-3 (Hu et al., 2015; Feng et al., 2019). Kukoamine A blocked N-Methyl-D-Aspartate Receptors (NMDARs), a key element involved in neuronal excitotoxicity (Hu et al., 2015). The neurotoxin 1-methyl-4-phenylpyridinium ion (MPP<sup>+</sup>) is used on SH-SY5Y dopaminergic neuroblastoma cells as an *in vitro* model of Parkinson's disease (PD). With this model, *cis*-feruloyltyramine isolated from *Nicandra physaloides* and kukoamine A were demonstrated to inhibit apoptosis in MPP<sup>+</sup>-induced cells and to promote autophagy (Wang et al., 2017a; Hu et al., 2017).

The neuroprotective properties of previously cited phenolamides has gained support from *in vivo* assays on PD murine models consisting of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

(MPTP) intoxicated mice. Indeed, the administration of kukoamine A, caffeoylphenylalanine and clovamide derivatives (from 10 to 20 mg/kg) alleviated the dyskinesia symptoms of these mice. These molecules also reduced apoptosis and oxidative stress and stimulated tyrosine hydroxylase accumulation, thereby supporting dopamine biosynthesis in the substantia nigra and striatum of mice, which are the brain areas especially affected in PD (Lim et al., 2015; Hu et al., 2017, 2018; Feng et al., 2019). Transgenic fruit flies (*Drosophila melanogaster*) over-producing Amyloid $\beta$  (A $\beta$ ) oligomers are used as a model of Alzheimer disease (AD) (Iijima et al., 2004). These transgenic flies exhibit several features of AD, including short-term memory loss, that can be quantified through a well-established aversive Pavlovian olfactory conditioning assay in which flies are trained to avoid an odour associated with an electric shock (Tully and Quinn, 1985). Whereas transgenic flies with AD symptoms did not avoid the odour associated with the electric shock, those fed with wolfberry kukoamine derivatives were preferentially attracted by the odour not associated with the electric shock, indicating a partial recovery of short-term memory (Zhou et al., 2016). This result is corroborated by the ability of wolfberry water extract to inhibit A $\beta$ 1-42 aggregation (Li and Yang, 2020). Recently, the oral administration of Avn-C to AD transgenic mice (Tg2576 and 5XFAD) was shown to partially restore their spatial memory capacities. Although the mechanisms remain unclear, the oral administration of Avn-C reduced caspase-3 cleavage, ameliorated neuroinflammation and increased the accumulation of IL-10 (Ramasamy et al., 2020).

## 6. Antioxidant properties

In addition to their capacity to modulate kinase cascade pathways, which in turn may increase the antioxidative potential of cells and organs (described above), phenolamides

have been described as efficient antioxidative and antiradical agents (Table 1). The characterisation of these properties has been documented in several studies using diverse assays assessing antiradical activities (DPPH, PTIO, ORAC,  $\cdot\text{OH}$ ,  $\cdot\text{O}_2^-$ ...) and metal chelating activity (Fe, Cu) (Choi et al., 2007, 2010; Gao et al., 2015; Lee et al., 2015; Abe et al., 2017; Xin et al., 2017; Spreng and Hofmann, 2018).

Interestingly, since phenolic acids, polyamines and aromatic amines are already known to be efficient antioxidative agents (Rice-Evans et al., 1996; Yen and Hsieh, 1997; Ha et al., 1998), their combination as phenolamides tends to potentiate this characteristic (Hadjipavlou-Litina et al., 2009; Abe et al., 2017; Kabanda, 2015). Several structure-function studies that focused on phenolamide subfamilies provided a better understanding of the structural features supporting their ROS-scavenging activity. Indeed, for dihydrocaffeoyl-spermine derivatives, referred as kukoamines, the position of the dihydrocaffeoyl moieties on the spermine nitrogens has a considerable impact on radical scavenging activity (DPPH test); kukoamine B ( $\text{N}^1, \text{N}^{10}$  bis DiHydroCaffeoyl spermine) and A ( $\text{N}^1, \text{N}^{14}$  bis DHC spermine) show higher activity than kukoamine C ( $\text{N}^5, \text{N}^{10}$  bis DHC spermine) and D ( $\text{N}^1, \text{N}^5$  bis DHC spermine) (Hadjipavlou-Litina et al., 2009). In addition, replacement of dihydrocaffeoyl moieties with caffeoyl moieties or feruloyl moieties shows the importance of chain flexibility in the DHC and the presence of hydroxyl groups on the phenolic ring (Hadjipavlou-Litina et al., 2009). In addition to their radical scavenging activity on DPPH, kukoamine A and B were found to be efficient scavengers of other radicals such as PTIO,  $\cdot\text{OH}$  and  $\cdot\text{O}_2^-$ , indicating several possible mechanisms including proton transfer, electron transfer, hydrogen atom transfer or radical adduct formation. In addition, these two compounds were also able to chelate iron (Li et al., 2018a). In the case of phenolamides integrating an aromatic amine (dopamine, tryptamine, tyramine, phenylethylamine), comparative analysis based radical scavenging activity (DPPH



assay) led to the conclusion that, among the phenolic moieties, the caffeoyl structure was the most efficient, whereas for the amine part, dopamine is most effective (Georgiev et al., 2012). The catechol function present in the amine part of dopamine is more effective than the catechol function on the feruloyl moieties in terms of sustaining electron transfer and, consequently, radical scavenging property (Kabanda, 2015).

## 7. Antimicrobial properties

Due to the constant increase in the number of infectious diseases and the concomitant lack of available treatments for certain diseases and antibiotic resistance, research and development into new antimicrobial agents is urgently needed to confront this major public health problem (Duval et al., 2019). The literature regarding the antimicrobial activities of phenolamide is relatively rare, and the methodology used to define the Minimum Inhibitory Concentration (MIC) is often different between studies and does not always follow international norms, which makes comparison difficult. To summarise the available data, we define three efficiency levels, based on the MIC categorisation (see details in Table 2). In a general way, phenolamides are mostly described as medium to low efficiency antimicrobial agents (Table 2). Regarding antibacterial activities, the most active compounds exhibiting a MIC value below 99 µg/mL were found against *Staphylococcus aureus* and *Streptococcus pyogenes* (Georgiev et al., 2012; Yingyongnarongkul et al., 2006, 2008). Dihydrocaffeoyl moieties appeared to be very important, as they to confer antibacterial activity against several strains of *S. aureus*, including methicillin resistant (MRSA) and vancomycin resistant (VRSA) strains (MIC < 50 µg/mL) (Yingyongnarongkul et al., 2006, 2008). Dihydrocaffeoyltyramine, *trans*-feruloyloctopamine and *trans*-feruloyltyramine, extracted from the root bark of *Lycium chinense* Mill., exhibited also significant antifungal activities (5

$\mu\text{g/mL} < \text{MIC} < 10 \mu\text{g/mL}$ ) against *Candida albicans*, *Saccharomyces cerevisiae* and *Trichosporon beigellii* (Lee et al., 2004).

Despite their generally moderate antimicrobial activity, the contribution of phenolamides in complex extracts exhibiting antimicrobial activities is still unclear and deserves better attention. Indeed, phenolamide-rich extracts such as *Lycium barbarum* and *Lycium chinense* leaf extracts also exhibited significant antibacterial activities against *Salmonella typhimurim* and *Escherichia coli* (Mocan et al., 2014). In addition, a study by Michalet et al. (2007) reported the capacity of N-trans-4'-methyldopamine, isolated from *Mirabilis jalapa*, to inhibit NorA multidrug efflux pumps overexpressed in *S. aureus*. Bacterial efflux pumps contribute to the multidrug resistance phenotype by extruding a wide range of exogenous compounds, including antibiotics (Hsieh et al., 1998). The use of efflux pumps inhibitors (EPI) could be an interesting strategy to restore antibiotic sensitivity to multidrug resistant strains. A structure-function analysis of this activity concluded that maximal NorA efflux pump inhibition was observed with phenolamides bearing two hydroxyl groups in the phenolic ring and an indolic group (Michalet et al., 2007).

The antimicrobial activity of phenolamides has also been extended to kinetoplastids. The latter represent a class of parasitic protists, with three of them causing major human tropical diseases: human African trypanosomiasis, Chagas disease and leishmaniasis. Research into new antikinetoplastids is highly active. Among the potential targets, identification of a trypanothione synthase inhibitor is promising, as reported in a recent review by Jagu et al. (2017). The trypanothione pathway regulates the redox potential in kinetoplastids. Trypanothione is synthesised by trypanothione synthase from two molecules of glutathione and one of spermidine. The design of trypanothione synthase inhibitors based on spermidine

analogues seems very promising (Jagu et al., 2017). In this context, kukoamine A and analogues have been successfully screened as trypanothione synthase inhibitors (Ponasik et al., 1995).

## 8. Anti-cancer properties

Cancer is one of the leading causes of death worldwide, with an estimated 18.1 million new cancer cases and 9.6 million deaths in 2018 (Bray et al., 2018). These indicators are still in progress due to many factors, including the increase in and ageing of the population, environmental impacts and socioeconomic development (Coyle, 2004; Hochberg and Noble, 2017). In high-income countries, the emergence cancer is slowly decreasing thanks to intensive research and innovation in the field in recent decades (Siegel et al., 2020). Nevertheless, the road is still long to find efficient treatments against the multiple forms of cancer, and the search for novel effective therapeutics is still needed.

The anticancer properties of phenolamides have been investigated and reported only for several metabolites and cancer types. According to Rocha et al. (2012), who reviewed the anticancer properties of hydroxycinnamic acids, these properties can be discriminated into three categories based on the mechanism of action: (i) blockade of the cell cycle, (ii) induction of apoptosis and (iii) inhibition of metastasis. Current knowledge on phenolamide anticancer activities is summarised in Table 3.

### *Breast cancer*

Breast cancer was the most diagnosed cancer among women worldwide in 2018 (Bray et al., 2018). Mitsis et al. (2018) identified *p*-coumaroylserotonin as a cytotoxic compound against a breast carcinoma cell line (MCF-7), which could act through multiple

pathways. Indeed, it blocked the cell cycle at the S-phase and induced apoptosis through caspase-8 activation. In addition, *p*-coumaroylserotonin decreased the accumulation of several cluster of differentiation (CD) markers like CD24, CD44, CD58 and CD71, all overexpressed in aggressive cancer cells with high metastasis potential. Avns purified from oat greatly impacted the viability of MDA-MB-231, another human breast cancer cell line. Among the major isoforms, AvnC was the most effective and acted through the induction of apoptosis (Hastings and Kenealey, 2017). Two synthetic Avns, i.e. Tranilast and dihydro-AvnD, also exhibited anticancer properties against breast tumour cell lines. The former inhibited cell growth and migration as well as colony formation in the BT6474 and MDA-MB-231 cell lines (Subramaniam et al., 2011). The latter decreased the invasion of MCF-7 cells by inhibiting the MAPK/NFκB and MAPK/AP-1 pathways and by suppressing Matrix Metalloproteinase 9 (MMP-9) expression (Lee et al., 2011).

### *Leukaemia*

Leukaemia is a cancer affecting blood cells. Several human leukaemia cell lines, namely U-937, Jurkat and HL-60, have been used as *in vitro* models to study the potential anticancer properties of tyramine- and putrescine-derived phenolamides. Among the tyramine-derived phenolamides, both caffeoyl and coumaroyl moieties exhibited anticancer activity, the former being the most effective (Park and Schoene, 2002, 2003). These two molecules induced cell cycle arrest at the S-phase and the induction of caspase-3 activity, indicating possible pro-apoptotic properties. In addition, caffeoyl- and *p*-coumaroyl-tyramines can inhibit the tyrosine kinase activity of the Epidermal Growth Factor Receptor (EGFR) involved in several signalling cascades leading to cell proliferation, invasion and metastasis. Among the polyphenolic compounds purified from corn bran,

diferuloylputrescine (DFP) was shown to be the most effective against the U-937 cell proliferation (Kim et al., 2014). DFP acted as an inducer of the apoptotic process which was characterised by chromatin condensation, DNA fragmentation, cytochrome *c* release and caspase-3 activation. Addition of DFP to the U-937 cell culture medium decreased the expression of anti-apoptotic markers such as Inhibitor of Apoptosis Protein (IAP) and the Bcl2 family proteins. Interestingly, DFP also exhibited pro-apoptotic properties against the Caki cell line, an *in vitro* model of kidney carcinoma. The active concentration against the cancer cell line (100  $\mu$ M) was not cytotoxic to normal human fibroblasts (Kim et al., 2014).

### *Brain cancer*

Among brain cancers, glioblastoma is certainly the most common but also the one with the worst prognosis (Lima et al., 2012). *p*-coumaroylserotonin, which was effective against MCF-7 breast cancer cells, was also successfully tested, together with feruloylserotonin, on the U251MG and T98G glioblastoma cell lines. *p*-coumaroylserotonin and feruloylserotonin reduced proliferation in the two cell lines by blocking the cell cycle at the G2/M and S phases and by triggering apoptosis (through the activation of caspase-8 in the case of *p*-coumaroylserotonin) and the collapse of mitochondrial membrane potential (Lazari et al., 2017; Alexiou et al., 2017). In addition, feruloylserotonin suppressed the expression of CD24 and CD44, two markers of cancer stem cells (Alexiou et al., 2017). *p*-coumaroylserotonin and feruloylserotonin were found to be non-toxic to zebrafish even at a high concentration (1 mM). The crude extract from *Lycium chinense* root bark also impacted glioblastoma cell growth. The active component of this crude extract is kukoamine A, which was able to block the cell cycle of U251 and WJ1 cell lines at G0-G1 phase. In addition, it had pro-apoptotic properties through a reduction in 5-LOX and Bcl2 expression, concomitant

with an increase in Bax and caspase-3 expression. Finally, kukoamine A also reduced cell migration and cell invasion by modulating the expression of specific markers such as C/EBP $\beta$ , N-cadherin, vimentin and TWIST at the protein level. Most interestingly, kukoamine A was successfully assayed *in vivo* in rats grafted with WJ1 glioblastoma cells. Repeated intra-peritoneal inoculation of kukoamine A at 10 mg/kg for 4 weeks led to a 30% reduction in tumour weight in comparison to control. This effect increase to a 50% reduction with kukoamine A at 20 mg/kg (Wang et al., 2016). The synthetic Avn Tranilast was also shown to be effective in reducing the proliferation, migration and invasiveness of the LN-18 and T98G malignant human glioma cell lines. Tranilast reduced DNA synthesis and blocked cells in the S phase. Moreover, it increased the accumulation of the CDK inhibitor p21 and reduced the production of Transformation Growth Factor (TGF)  $\beta$ 1 and  $\beta$ 2. Moreover, oral administration of Tranilast (200 mg/kg) was able to inhibit glioma growth in the 9L rat glioma model, where cells were implanted intracranially in syngeneic Fisher 344 rats. Tranilast treatment significantly decreased the glioma volume after 10 days (Platten et al., 2001).

### *Digestive cancers*

Among the phenolamides, Avns have been reported to exhibit anticancer activities against several digestive cancers. Indeed, natural and synthetic Avns can inhibit cell proliferation in several colon (HT29, Caco-2, LS174T, HCT116), hepatic (HepB3) and pancreatic (PGHAM-1) cancer cell lines (Hiroi et al., 2002; Guo et al., 2010; Scarpa et al., 2018; Wu et al., 2018; Turrini et al., 2019). In the Caco-2 and HepB3 cell lines, Avns induced the activation of caspase-8 and -3. Avns were also able to inhibit COX-2 activity and PGE2 production, which could contribute at least partly to the inhibition of proliferation in these cell lines (Guo et al., 2010; Scarpa et al., 2018). Recently, the combined use of colon cancer

cell lines (HCT116, HCT8, DLD1) and colorectal carcinogenesis murine models (azoxymethane/dextran sulphate sodium-induced colorectal cancer, a xenograft tumour model in BALB/c nude mice) led to the identification of at least two molecular mechanisms and signalling pathways by which AvnA impacts colorectal cancer (Fu et al., 2019a, 2019b). Indeed, AvnA appeared to activate cellular senescence through the increased expression of the microRNA miR-129-3p, which repressed the expression of the E3 ubiquitin ligase Pirh2 (p53-induced RING-H2), Insulin like Growth Factor 2 mRNA Binding Protein 3 (IGF2BP3) and CDK6. As a consequence of Pirh2 repression, the p53 and p21 protein levels increased inducing cell senescence (Fu et al., 2019b). In addition, AvnA also inhibited the ATPase activity of DEAD-Box helicase 3 (DDX3) (Fu et al., 2019a), which is involved in the cell invasiveness in several cancer types (Bol et al., 2015). The impact of Avns in limiting cancer invasiveness has also been demonstrated through the inhibition of migration and epithelial-mesenchymal transition (EMT) in tumour cells. Indeed, yeast-derived *N-(E)-p-coumaroyl-3-hydroxyanthranilic acid* and *N-(E)-caffeoyl-3-hydroxyanthranilic acid* reduced the expression of the zinc finger protein Snail1 and lymphoid-enhancing factor-1 (LEF-1), which led to a reduction in E-cadherin expression, a major molecule implicated in the EMT process (Finetti et al., 2018). *N-trans-feruloyloctopamine* also exhibited robust inhibition of cell proliferation and invasion in hepatocellular carcinoma cells (HCCLM3 and Huh7), and may act *via* the down-regulation of Slug expression and p38 MAPK and Akt phosphorylation (Bai et al., 2017).

## 9. Phenolamides in cosmetics

In the cosmetics industry, skin whitening products represent an important sector, with an estimation of 15% of the world population concerned

([www.sironabiochem.com/products/skinlightening](http://www.sironabiochem.com/products/skinlightening)). Skin pigmentation is due to the accumulation of melanin produced by melanocytes in the epidermis. Melanogenesis, the biosynthetic pathway leading to melanin, is quite well-characterised. Tyrosinase is a multi-functional enzyme catalysing the two first steps of melanogenesis, namely the hydroxylation of L-tyrosine to L-DOPA, followed by its oxidation into dopaquinone (Hearing and Jiménez, 1987). This crucial role of tyrosinase in melanogenesis makes it a preferential target to inhibit melanogenesis. Hence, most commercial skin whitening products contain a tyrosinase inhibitor as the active principle. The search for tyrosinase inhibitors of natural origin is an active topic, as highlighted in a recent review by Pillaiyar et al. (2017) who listed potentially effective candidates. Among them, many phenolic compounds are mentioned (flavonoids, coumarins, resveratrol derivatives). Although phenolamides were not mentioned, several of them presented tyrosinase inhibitory effects in different assays.

Ethyl acetate and methanol extracts of safflower seeds exhibit strong mushroom tyrosinase inhibitory activity (Roh et al., 2004). Feruloylserotonin and *p*-coumaroylserotonin have been shown to be the active compounds in safflower seed extract, with IC<sub>50</sub> values of 23 and 74  $\mu$ M, respectively (Table 4). Both molecules were able to inhibit melanin synthesis in murine B16 melanoma cells with IC<sub>50</sub> values far below the cytotoxic concentration. Serotonin-composed phenolamides have also been highlighted as effective inhibitors of murine and human tyrosinase in a structure-function study comparing 19 structural derivatives (Yamazaki et al., 2009). Indeed, serotonin (5-hydro-indole) moieties confer better tyrosinase inhibitor activity than tyramine and tryptamine moieties. The number of hydroxyl groups on the phenolic moieties is also an important factor. This assay identified two compounds, i.e. *N-trans*-caffeoylserotonin and *N-trans*-protocachuoylserotonin, as the most potent tyrosinase inhibitors. Interestingly, *N-trans*-protocachuoylserotonin exerted non-competitive



inhibition on tyrosinase activity. Tyramine-composed phenolamides have been screened as human tyrosinase inhibitors. The three best inhibitors are *N-trans*-caffeoyltyramine, *N*-dihydrocaffeoyltyramine and *N*-dihydrocoumaroyltyramine, highlighting once again the importance of hydroxyl groups on the phenolic ring to support this property (Okombi et al., 2006). The mechanism of action has not been deeply investigated; however, the authors did not find a correlation between antiradical activity and tyrosinase inhibitory capacity, ruling out the possibility that these compounds act as antioxidants against dopaquinone, the final product of tyrosinase. The use of these three compounds as tyrosinase inhibitors is now under patent (Okombi et al., 2013, 2015). Interestingly, *N-trans*-feruloyltyramine was found as the active component in alcoholic extracts of *Enicosanthum membranifolium* branches and *Aurea helianthus* stems, which inhibited melanogenesis in the murine B16 melanoma cell line (Efdi et al., 2007; Kim et al., 2018c). *N-trans*-feruloyltyramine did not act as an inhibitor of tyrosinase activity but rather reduced tyrosinase accumulation (Efdi et al., 2007). Melanogenesis inhibition is not restricted to indolic and aromatic monoamine phenolamides. Indeed, polyamine phenolamides from corn bran and the pollen of *Quercus mongolica* also displayed inhibitory activity against mushroom tyrosinase (Choi et al., 2007; Kim et al., 2018b). Among the derivatives tested, those bearing a long polyamine chain (spermidine and spermine) with three to four hydroxycinnamic acids exhibited the highest inhibitory activity.

## 10. Bioavailability

Whereas bioavailability and bioaccessibility have been well-documented and reviewed for certain categories of phenolic compounds, including flavanones (Khan et al., 2014) and phenolic acids (Pei et al., 2016; Zhao and Moghadasian, 2010), studies specifically focused on

phenolamides are still rare. The bioavailability of Avns is probably the most studied. Indeed, the three major Avns from oat (AvnA, B and C) appear in the blood plasma of human adults 15 min after Avns skim milk supplementation, and reach a peak after 2 h (Chen et al., 2007). Interestingly, the occurrence of Avns in plasma was accompanied by an increase in reduced glutathione in blood plasma, which is an important antioxidant component (Chen et al., 2007). The bioavailability of AvnA in human blood plasma is 2 to 5 times higher than that of AvnB and C (Chen et al., 2007). The same observation was also made in rat blood plasma (Koenig et al., 2011). Bioavailability also depends on the organ considered, since AvnB was the major form found in the liver and AvnC was the major form found in skeletal muscles (Koenig et al., 2011). Metabolites absorbed by the animal or human body are prone to modifications such as conjugation with sulphates or glucuronides, or metabolism by the gut microbiota (Gonzalez-Manzano et al., 2009). Indeed, phenolamides found in the blood plasma and organs of rat fed with Avns or serotonin-derivative phenolamides were mainly in conjugated forms (from 50% up to 99%) (Koyama et al., 2006; Koenig et al., 2011). Interestingly, Wang and coworkers (2015) identified the biotransformed products of AvnC in the mouse and human gut microbiota and demonstrated that one metabolite of AvnC (dihydro AvnC) was more effective than AvnC itself in terms of limiting the proliferation of the human HCT-116 colon cancer cell line (Wang et al., 2015). These results highlight the importance of such metabolites and the constituents of the gut microbiota.

## 11. Chemical synthesis and biological production

As for many plant specialized metabolites, phenolamides may constitute a limited resource, due to the fact that they are usually present at low concentrations in plants, or found at high concentrations in very specific organs. Their extraction may lead to low yield and/or need a

multi-step process that can be time-consuming and expensive. These findings may constitute a bottleneck to the use of these wide-range bioactive compounds for pharmaceutical applications. Several reports describe possible pathways to their chemical synthesis (Garnelis et al., 2005; Yingyongnarongkul et al., 2006, 2008). Chemical synthesis is usually regarded as a multi-step and costly process using non-renewable resources. Since the early 2000s, the availability of genetic sequences coding for acyltransferases involved in the biosynthesis of different phenolamide classes has allowed for the development of biotechnological approaches. Indeed, acyltransferases catalyse the last step of phenolamide synthesis, consisting of transferring acyl chains under the form of coA esters (commonly cinnamoyl-coA, *p*-coumaroyl-coA, caffeoyl-coA, feruloyl-coA, sinapoyl-coA) onto the N atom of aromatic monoamines or polyamines. Several transferases have been characterised from plants, usually bearing a specificity for the amine type with more flexibility on the acyl chain. Hence, tyramine-hydroxycinnamoyl-transferase (THT) isolated notably from various Solanaceae is able to synthesise tyramine-associated phenolamides with coumaroyl-coA or feruloyl-coA (Schmidt et al., 1999; Farmer et al., 1999; Roepenack-Lahaye et al., 2003b; Kang et al., 2006). Other transferases like serotonin-hydroxycinnamoyl-transferase (SHT), agmatine-hydroxycinnamoyl-transferase and spermidine-hydroxycinnamoyl-transferase have been characterised and cloned from different plant species (Luo et al., 2009; Muroi et al., 2009; Onkokesung et al., 2012; Elejalde-Palmett et al., 2015; Tanabe et al., 2016; Peng et al., 2016; Delporte et al., 2018; Ube et al., 2019). This catalogue of hydroxycinnamoyl transferases, together with their flexibility regarding the acyl donor origin, allows *a priori* the possibility to synthesise a large array of phenolamides.

The impact of overexpressing acyltransferases on phenolamide accumulation has been investigated in several plant models with contrasting results. Indeed, neither the

overexpression of the pepper SHT in rice, nor the overexpression of the endogenous THT of tobacco led to the expected constitutive accumulation of serotonin- and tyramine-associated phenolamides (Jang et al., 2004; Hagel and Facchini, 2005). In the case of the transgenic plants overexpressing the pepper SHT, addition of tyramine to the culture medium led to an increase in phenolamide accumulation in comparison to the wild type plant. This supports the idea that the endogenous concentrations of serotonin and tyramine could constitute a bottleneck. Accordingly, the overexpression of pepper SHT and tomato THT in tomato plants, known to accumulate high concentrations of endogenous tyramine and serotonin, increased the constitutive accumulation of phenolamides by a factor 2 to 10 (Kang et al., 2009a; Campos et al., 2014). Nevertheless, with this strategy, the accumulation level of phenolamides remains too low (from ng/g to hundred  $\mu\text{g/g}$  of fresh weight) to envision using them as a production platform (Table 5).

Phenolamide production has been investigated through metabolic engineering in microorganisms *i.e.* yeast and bacteria. Microorganisms are unable to produce hydroxycinnamoyl-coA esters. The plant specific 4-coumarate-coA ligase (4CL) catalyses the formation of the hydroxycinnamoyl-coA esters from hydroxycinnamic acids and coenzyme A. Co-expression of 4CL and acyltransferases was successfully developed to produce a high diversity of phenolamides in microorganisms. In yeast (*S. cerevisiae*), Moglia et al. (2010, 2015) developed a strain coexpressing 4CL2 from tobacco and hydroxycinnamoyl coA transferase from globe artichoke (HCT) producing anthranilate-based phenolamides from phenolic acids and anthranilate supplemented to the growth medium. Using the same strategy, Eudes et al. (2016) built up yeast strains able to produce agmatine, putrescine, spermidine and spermine derivatives. More recently, Bouchez et al. (2019) reported on the production of clovamide and its derivatives by a yeast strain co-expressing 4CL5 from *Arabidopsis thaliana* and

hydroxycinnamoyl-CoA: L-3,4-dihydroxyphenylalanine hydroxycinnamoyl transferase (HDT) from clover. Interestingly, depending on the acyl donors and acceptors added to the cell culture medium, the strain could synthesise up to 22 different phenolamides. The same genes were also successfully expressed in the bacterial strain *Lactococcus lactis* (Bouchez et al., 2019). The bacteria *E. coli* has been also used for the production of tyramine-, serotonin- and phenethylamine-based phenolamides with strains co-expressing 4CL and either SHT (Kang and Back, 2009; Sim et al., 2015; Song et al., 2017) or THT (Kang et al., 2009b; Sim et al., 2015). As for the yeast system, the *E. coli* expression system has the advantage of directly producing the molecule of interest in the culture medium, but with higher production levels than with yeast. In addition, in order to avoid the addition of the substrate (phenolic acids and amines) into the culture medium, Sim et al. (2015) built up a strain combining the overexpression of 4CL and THT together with a tyrosine decarboxylase (TDC) and a tyrosine ammonia lyase (TAL), which led to the production of endogenous tyramine and *p*-coumaric acid from tyrosine. As a consequence, this strain was able to produce *p*-coumaroyl-tyramine directly from glucose.

## 12. Conclusions

Since their first discovery as bioactive compounds in the 1970s (Dorer et al., 1974; Funayama et al., 1980), phenolamides have been of interest in a pharmacological context. Indeed, our review led us to identify about 100 phenolamide structures exhibiting activity. Ranking these structures based on their amine moieties shows that some of them (putrescine, spermidine, tyramine derivatives and clovamide) have been successfully characterised regarding a broad panel of bioactivities (Fig. 3), whereas others exhibited more specific bioactivities (or have been assayed and only specific bioactivities have been reported). Phenolamide structural

diversity is far broader than the actual reported structures, since theoretical structure generation based on the most common phenolic and amines moieties can reach several hundreds (Li et al., 2018b). Therefore, the potential to discover new bioactivities among this family of metabolites is huge. Increased research efforts to prospect their bioactivity is fully justified by the major associated issues, in terms of human and plant health.

## Figure captions

**Fig. 1: Structural origin of phenolamide and representation of major structures**

**Fig. 2: Molecular targets mediating the anti-inflammatory properties of phenolamides in macrophage, dermal fibroblast and neuronal cell models.** Inflammatory stimuli induce kinase cascades involving JNK (c-Jun N-terminal kinase) and ERK (extracellular signal regulated kinase), which induce the nuclear translocation of NF $\kappa$ B and the activation of the AP1 (activator protein 1) transcription factor. As a consequence, the transcription of iNOS (inducible nitrite oxide synthase), COX2 (cyclooxygenase 2), IL (interleukin)-1, -6, -8 and TNF $\alpha$  (tumor necrosis factor  $\alpha$ ) is induced. The steps that are inhibited by phenolamides are represented in the scheme. The colour code indicates if it has been described in macrophages (green), dermal fibroblasts (grey) or neuronal (red) cells. CoD: p-coumaroyldopamine; FT: feruloyltyramine; DHCT: dihydrocaffeoyltyramine; DCP: dicoumaroylputrescine; DFP: diferuloylputrescine; CVD: clovamide; Avns: avenanthramides

**Fig. 3: Summary of phenolamide bioactivities according to their amine moiety.** For each phenolamide class, colours indicate that at least one structure has been reported for the related bioactivity. MS: metabolic syndrome; VS: vascular system; AL: anti-inflammatory; NP: neuroprotection; AO: antioxidant; AM: antimicrobial; AC: anticancer; C: cosmetic.

## Tables

**Table 1: Antioxidant properties of phenolamides reported in the literature.**

Molecules	DPPH scavenging activity (%)	EC <sub>50</sub> (μM)					References
		PTIO <sup>•-</sup> scavenging	Cu <sup>2+</sup> reduction	DPPH scavenging	O <sub>2</sub> <sup>•-</sup> scavenging	OH <sup>•</sup> scavenging	
<i>N</i> -E-coumaroyltyramine	96						Gao 2015
<i>N</i> -E-feruloyltyramine	96						
Lyciumamide A	76						
Lyciumamide B	73						
Lyciumamide C	90						
Kukoamine A		119	10	87	401	168	Xican et al. 2018
Kukoamine B		29	9	74	278	147	
Kukoamine A	96						Hadjipavlou-Litina et al., 2009
Kukoamine B	97						
Kukoamine C	0						
Kukoamine D	42						
Di-coumaroylputrescine				>500	>10000	165	Choi et al., 2007
Di-feruloylputrescine				38	292	352	
Coumaroyl-feruloylputrescine				70	488	193	
<i>N</i> - <i>trans</i> -feruloyl- <i>N'</i> - <i>cis</i> -feruloyl-cadaverine				>100			Xin et al., 2017
<i>N,N'</i> - <i>trans</i> -diferuloyl-3-oxo-cadaverine				>100			
<i>N</i> - <i>trans</i> -feruloyl- <i>N'</i> - <i>cis</i> -feruloyl-3-hydroxy-cadaverine				37			
<i>N,N'</i> - <i>cis</i> -diferuloyl-3-hydroxy-cadaverine				>100			
<i>N</i> - <i>trans</i> - <i>p</i> -coumaroyl- <i>N'</i> - <i>trans</i> -feruloyl-3-hydroxy-cadaverine				>100			
Diferuloylcadaverine				38			
<i>N,N'</i> -Diferuloylputrescine				41			
( <i>E,Z</i> )-Terrestribisamide				>100			
( <i>Z,Z</i> )-Terrestribisamide				67			
<i>N</i> - <i>trans</i> - <i>o</i> -coumaroyldopamine	78			28			
<i>N</i> - <i>trans</i> - <i>m</i> -coumaroyldopamine	74			36			
<i>N</i> - <i>trans</i> -feruloyldopamine	73			45			
<i>N</i> - <i>trans</i> - <i>p</i> -coumaroyldopamine	24			406			
<i>N</i> - <i>trans</i> -feruloyl-3-methyldopamine	64			70			
<i>N</i> - <i>trans</i> -feruloyl-4-methyldopamine	43			165			



<i>N-trans</i> -isoferuloyl-dopamine	76			35			
<i>N-trans</i> -isoferuloyl-3-methyldopamine	45			155			
<i>N-trans</i> -isoferuloyl-4-methyldopamine	33			288			
<i>N-trans-o</i> -coumaroyl-3-methyldopamine	39			217			
<i>N-trans-m</i> -coumaroyl-3-methyldopamine	31			874			
<i>N-trans-p</i> -coumaroyl-3-methyldopamine	34			279			
<i>N-trans-o</i> -coumaroyl-4-methyldopamine	28			348			
<i>N-trans-m</i> -coumaroyl-4-methyldopamine	34			279			
<i>N-trans-p</i> -coumaroyl-3-methyldopamine	38			225			

- Table 2A/B: Antimicrobial activities of phenolamides.** The efficiency is represented by symbols defining three categories: +++ MIC <50 µg/mL; ++ 50<MIC<99 µg/mL; + MIC >100 µg/mL. References are given by superscript letters. *a* Georgiev et al., 2012; *b* Yingyongnarongku et al., 2006; *c* Yingyongnarongku et al., 2008; *d* Voynikov et al., 2016; *e* Lee et al., 2004; *f* Kyselka et al., 2018.

4 **Table 2A represents available data on antibacterial activities.**

Molecules	<i>B. subtilis</i> 1A95 <sup>a</sup>	<i>L. monocytogenes</i> C12 <sup>a</sup>	<i>S. aureus</i> 209 <sup>a</sup>	<i>S. pyogenes</i> 10535 <sup>a</sup>	<i>S. aureus</i> NBIMCC 3359 <sup>d</sup>	<i>S. aureus</i> ATCC 6538P <sup>d</sup>	<i>S. aureus</i> MRSA <sup>b,c</sup>	<i>S. aureus</i> MRSA 20628 <sup>b,c</sup>	<i>S. aureus</i> MRSA 20630 <sup>b,c</sup>	<i>S. aureus</i> MRSA 20631 <sup>b,c</sup>	<i>S. aureus</i> MRSA 20632 <sup>b,c</sup>	<i>S. aureus</i> MRSA 20633 <sup>b,c</sup>	<i>S. aureus</i> MRSA 20635 <sup>b,c</sup>	<i>S. aureus</i> MRSA 20636 <sup>b,c</sup>	<i>S. aureus</i> MRSA 20652 <sup>b,c</sup>	<i>S. aureus</i> MRSA 20653 <sup>b,c</sup>	<i>S. aureus</i> MRSA 20654 <sup>b,c</sup>	<i>S. aureus</i> VRSa 20622 <sup>b,c</sup>	<i>S. aureus</i> VRSa 20623 <sup>b,c</sup>	<i>S. aureus</i> VRSa 20624 <sup>b,c</sup>	<i>S. aureus</i> VRSa 21083 <sup>b,c</sup>
Dihydrocaffeoylpropanediamine							++	++	++	++	++	++	+++	+++	+	+++	++	+	++	++	+++
Dihydrocaffeoylputrescine							+++	++	++	+++	+++	+++	+++	+++	+	+++	+++	+	+++	+++	+++
Dihydrocaffeoylcadaverine							++	++	++	++	++	++	+++	++	++	++	++	++	+++	++	+++
Dihydrocaffeoylhexanediamine							+	++	++	++	++	++	+++	++	+	+++	+++	+	++	++	+++
<i>N</i> 1- <i>N</i> 9-Bis(dihydrocaffeoyl)norspermidine							++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
<i>N</i> 1- <i>N</i> 10-Bis(dihydrocaffeoyl)spermidine							++	+++	+++	++	++	+++	++	+++	+++	+++	+++	+++	+++	+++	+++
Kukoamine A							+++	++	++	++	++	++	++	++	++	++	++	+++	++	++	+++
Tri(dihydrocaffeoyl)spermine							+	++	++	++	++	++	++	++	++	+++	++	++	++	++	+++
Tetra(dihydrocaffeoyl)polyamine							+++	+++	+++	+++	+++	+++	+++	+++	++	+++	+++	++	+++	+++	+++
Caffeoyllysine					+	+															
Cinnamoyldopamine	+	+	+	+																	
Coumaroyldopamine	+	+	+	+																	
Caffeoylphenylethylamine	+	+	+	+																	
Caffeoyldopamine	+	+	+	+																	
Caffeoyltyramine	+	+	+	+																	
Caffeoyltryptamine	+	+	+	++																	
Feruloyldopamine	+	+	++	+																	
Feruloyltyramine	+	+	++	+																	
Feruloyltryptamine	+	+	+	+																	
Sinapoyldopamine	+	+	+	+																	
Sinapoyltyramine	+	+	++	++																	
Sinapoyltryptamine	+	+	+	++																	

5 **Table 2B represents antifungal activities.**

Molecules	<i>C. albicans</i> 62 <sup>a</sup>	<i>F. culmorum</i> DMF0103 <sup>f</sup>	<i>P. verrucosum</i> DMF 0023 <sup>f</sup>	<i>A. niger</i> CCM8189 <sup>f</sup>	<i>C. albicans</i> <sup>e</sup>	<i>S. cerevisiae</i> <sup>e</sup>	<i>T. beigeli</i> <sup>e</sup>
Dihydro- <i>N</i> -caffeoyltyramine					+++	+++	+++
<i>Trans-N</i> -feruloyloctopamine					+++	+++	+++
<i>Trans-N</i> -caffeoyltyramine	+				+++	+++	+++
<i>Cis-N</i> -caffeoyltyramine					+++	+++	+++
<i>p</i> -Coumaroylputrescine		+	+	+			
Feruloylputrescine		+	+	+			
<i>N,N'</i> -di- <i>p</i> -coumaroylputrescine		+	+	+			
Di and Tri <i>p</i> -coumaroylspermidine		+	+	+			
Cinnamoyldopamine	+						
Coumaroyldopamine	+						
Caffeoylphenylethylamine	+						
Caffeoyldopamine	+						
Caffeoyltryptamine	+						
Feruloyldopamine	+						
Feruloyltyramine	+						
Feruloyltryptamine	+						
Sinapoyldopamine	+						
Sinapoyltyramine	+						
Sinapoyltryptamine	+						

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10 **Table 3: Anticancer properties of phenolamides reported in the literature.**

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Molecules	Cancer type	Model	Cell cycle arrest properties	Pro-apoptosis properties	Anti-metastasis properties	References
<i>p</i> -Coumaroylserotonin	Brain	U251MG T98G	Blocks cells at G2/M and S phases	Induces caspase-8 Induces mitochondrial membrane depolarisation		Lazari et al., 2017
Feruloylserotonin	Brain	U251MG T98G	Blocks cells at G2/M and S phases	Induces caspase-8 Induces mitochondrial membrane depolarisation	Reduces the expression of CD24 and CD44	Alexiou et al., 2017
Grossamide and methylgrossamide	Brain	GSC-3# GSC-12#				Zhu et al., 2017
Kukoamine A	Brain	U251 WJ1	Blocks cells at G0/G1- phase	Reduces 5-LOX and Bcl2 expression level Increases Bax and caspase-3 expression level	Reduces C/EBP $\beta$ , N-cadherin, vimentin, Twist, Snail, Slug expression Increases E-cadherin expression level Reduces 5-LOX expression level Inhibits cell migration Inhibits cell invasion	Wang et al., 2016
Tranilast	Brain	LN18 T98G 9L Rat	Blocks cells at S phase Increases the cellular level of p21		Inhibits the release of TGF- $\beta$ 1 and TGF- $\beta$ 2 Inhibits cell migration and invasiveness Decreases the size of the tumour <i>in vivo</i> Decreases MMP-2 activity	Platten et al., 2001
<i>p</i> -Coumaroyltyramine	Leukaemia	HL60 U937 Jurkat	Blocks cells at S-phase Inhibits tyrosinase activity of EGFR	Induces caspase-3		Park and Schoene, 2002, 2003
Caffeoyltyramine	Leukaemia	HL60 U937 Jurkat	Blocks cells at S-phase Inhibits tyrosinase activity of EGFR	Induces caspase-3 Induces DNA fragmentation		Park and Schoene, 2003
Di-feruloylputrescine	Leukaemia	U937		Decreases the expression of cIAP2, XIAP, Induces the cleavage of PLC-g and PARP Induces the release of cytochrome c Induces chromatin condensation Induces DNA fragmentation Bcl2, Mcl-1 and pro-caspase 3 Inhibits NF $\kappa$ B promoter activity		Kim et al., 2014

<i>p</i> -Coumaroylserotonin	Breast	MCF-7	Blocks cells at S-phase	Induces Caspase-8	Reduces the CD24, CD44, CD58 and CD71 expression level	Mitsis et al., 2018
Avenanthramide C	Breast	MDA-MB-231	Blocks cells at subG1 phase	Induces DNA fragmentation Induces apoptosis Induces caspase 3 and 7 activity		Hastings and Kenealey, 2017
Tranilast	Breast	MDA-MB-231 BT-474		Induces the cleavage of PARP	Reduces the accumulation of MRTF-A Reduces the clonogenicity of cells Inhibits cell migration	Subramaniam et al., 2011
Dihydro-avenanthramide D	Breast	MCF-7			Blocks the induction of MMP-9 protein and its excretion Inhibits NFκB and AP-1 activation Inhibits the JNK pathway Inhibits the ERK pathway	Lee et al., 2011
Di-feruloylputrescine	Kidney	Caki		Induces apoptosis		Kim et al., 2014
Tranilast	Pancreas	PGHAM-1	Blocks cells at G0-G1 phase		Decreases angiogenesis in dorsal air sac models	Hiroi et al., 2002
Natural and synthetic avenanthramides	Colon	Caco-2; HCT116; HCT8; HT29		Induces caspase-2, -3, -8 activities AvnA increases miR-129-3p expression AvnA induces p53 and p21 protein accumulation	Inhibits expression of hTERT, COX-2 and MDR1 Inhibits COX-2 activity Reduces PGE <sub>2</sub> production AvnA inhibits DDX3 ATP hydrolysis activity Inhibits Snail1 and E-cadherin expression	Guo et al., 2010 Scarpa et al., 2018 Fu et al., 2019 a, b Finetti et al., 2018
Natural and synthetic avenanthramides	Liver	Hep3B		Induces caspase-2, -3, -8 activities	Inhibits expression of hTERT, COX-2 and MDR1 Inhibits COX-2 activity Reduces PGE <sub>2</sub> production	Scarpa et al., 2018
N-feruloyloctopamine	Liver	Huh7, HCCLM3			Inhibits p38 MAPK and Akt phosphorylation Inhibits Slug expression Increases E-cadherin expression	Bai et al., 2017

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15 **Table 4: Summary of the antimelanogenic properties of phenolamides.** The IC<sub>50</sub> values for  
 16 mushroom, murine tyrosinase activity and melanin production are given in micromolar. The  
 17 inhibition of human tyrosinase in melanoma cells is given as % for a phenolamide  
 18 concentration of 100 μM.

Molecules	Mushroom Tyr Inhibition IC <sub>50</sub>	B16 Tyr (L-DOPA) Inhibition IC <sub>50</sub>	B16 Tyr (TYR) inhibition IC <sub>50</sub>	B16 melanin inhibition IC <sub>50</sub>	Human HMVII melanoma cell Tyr inhibition	References
<i>N1-(E)-N6-(Z)-di-p-coumaroylputrescine</i>	75.1					Kim et al., 2018
<i>N1-acetyl-N5, N10-(E)-di-p-methoxy-coumaroylspermidine</i>	>100					
<i>N1-acetyl-N5 (Z), N10-(E)-di-p-methoxy-coumaroylspermidine</i>	>100					
<i>N1-acetyl-N5, N10-(Z)-di-p-methoxy-coumaroylspermidine</i>	>100					
<i>N1, N5, N10-(E)-tri-p-coumaroylspermidine</i>	20.3					
Safflospersmidine A	85.8					
<i>N1, N5, N10-(Z)-tri-p-methoxy-coumaroylspermidine</i>	>100					
<i>N1, N5-(Z), N10-(E)-tri-p-coumaroylspermidine</i>	31.7					
<i>N1, N5, N10-(Z)-tri-p-coumaroylspermidine</i>	85.8					
<i>N1, N10-(E) di-p-coumaroyl-N5-(Z)-caffeoylspermidine</i>	24.7					
<i>N1-(E)-, N10-(Z) di-p-coumaroyl-N5-(Z)-caffeoylspermidine</i>	21.5					
<i>N1-(E)-p-coumaroyl-N5 (Z) N10 (E)-di-caffeoylspermidine</i>	18.9					
<i>N1, N5-(E)-di-caffeoyl-N10 (E) p-coumaroylspermidine</i>	60.4					
<i>N1, N5, N10-(E)-tri-caffeoylspermidine</i>	24.6					
<i>N1, N5 (E), N10-(Z)-tri-caffeoylspermidine</i>	80.3					
<i>N1-p-methoxybenzoyl-N5 (Z)-N10 (E)-di-p-methoxy-coumaroylspermidine</i>	>100					
<i>N1, N5, N10, N14-(Z)-tetra-p-coumaroylspermine</i>	19.5					
<i>N-p-coumaroylserotonin</i>	74			245		Roh et al., 2004
<i>N,N'-di-coumaroylputrescine</i>	82.4	181.7	1056.7	3169.5		Kim et al., 2018; Choi et al., 2007
<i>N-p-coumaroyl-N'-feruloylputrescine</i>		233.6	921.5	1257.6		Choi et al., 2007
<i>N,N'-di-feruloylputrescine</i>		291.3		733.6		Choi et al., 2007
<i>N-trans-feruloyltyramine</i>				<10		Efdi et al., 2007
<i>N-trans-caffeoyltyramine</i>		-		-	30	Yamazaki et al., 2009
<i>N-trans-caffeoyltryptamine</i>		-		-	14	Yamazaki et al., 2009
<i>N-trans-caffeoylserotonin</i>		28		15	55	Yamazaki et al., 2009
<i>N-trans-caffeoyl-methoxy-tryptamine</i>		-		-	4	Yamazaki et al., 2009
<i>N-trans-feruloyltryptamine</i>		-		>30	13	Yamazaki et al., 2009
<i>N-trans-feruloylserotonin</i>	23	216		23; 191	48	Yamazaki et al., 2009; Roh et al., 2004

<i>N-trans</i> -protocatcheuoyltyramine		-		-	9	Yamazaki et al., 2009
<i>N-trans</i> -protocatcheuoyltryptamine		-		-	7	Yamazaki et al., 2009
<i>N-trans</i> -protocatcheuoylserotonin		73		3	43	Yamazaki et al., 2009
<i>N-trans</i> -resorcinoylserotonin		42		15	39	Yamazaki et al., 2009
<i>N-trans</i> -guaiacoylserotonin		211		>30	16	Yamazaki et al., 2009
<i>N-trans</i> -hydroxybenzoyltryptamine		-		>30	0	Yamazaki et al., 2009
<i>N-trans</i> -hydroxybenzoylserotonin		233		>30	9	Yamazaki et al., 2009
<i>N-trans</i> -benzoyltryptamine		-		-	1	Yamazaki et al., 2009
<i>N-trans</i> -benzoylserotonin		333		>30	23	Yamazaki et al., 2009
<i>N</i> -acetylserotonin		311		>30	18	Yamazaki et al., 2009
Serotonin		550		>30	15	Yamazaki et al., 2009
5-Hydroxyindole		68		13	54	Yamazaki et al., 2009





<i>E. coli</i>	<i>Os4CL-CaSHT</i>	<i>p</i> -coumaric acid + PHEA Caffeic acid + PHEA Ferulic acid + PHEA Cinnamic acid + PHEA 3-methoxycinnamic acid + PHEA 4-methoxycinnamic acid + PHEA	<i>p</i> -coumaroylphenethylamine Caffeoylphenethylamine Feruloylphenethylamine Cinnamoylphenethylamine 3-methoxycinnamoylphenethylamine 4-methoxycinnamoylphenethylamine	- - - - - -	Sim et al., 2015
	<i>Os4CL-CaTHT</i>	<i>p</i> -coumaric acid + TYR <i>m</i> -coumaric acid + TYR <i>o</i> -coumaric acid + TYR Caffeic acid + TYR Ferulic acid + TYR Cinnamic acid + TYR 3-methoxycinnamic acid + TYR 4-methoxycinnamic acid + TYR	<i>p</i> -coumaroylptyramine <i>m</i> -coumaroylptyramine <i>o</i> -coumaroylptyramine Caffeoyltyramine Feruloyltyramine Cinnamoyltyramine 3-methoxycinnamoyltyramine 4-methoxycinnamoyltyramine	- - - - - - - -	Sim et al., 2015
	<i>Os4CL-CaSHT-PpPDC</i>	<i>p</i> -coumaric acid + PHEA	<i>p</i> -coumaroylphenethylamine	101.9 mg/L	
	<i>Os4CL-CaSHT-SeTAL-Pp-PDC-aroG<sup>fbr</sup>-tyrA<sup>fbr</sup></i>	<i>p</i> -coumaric acid + PHEA	<i>p</i> -coumaroylphenethylamine	152.5 mg/L	
	<i>Os4CL-CaTHT-PcTDC</i>	<i>p</i> -coumaric acid + TYR	<i>p</i> -coumaroylptyramine	48.2 mg/L	
	<i>Os4CL-CaTHT-PcTDC-aroGfbr-tyrAfbr</i>	<i>p</i> -coumaric acid + TYR	<i>p</i> -coumaroylptyramine	495.4 mg/L	
	<i>Os4CL-CaTHT-PcTDC-aroGfbr-SeTAL-tyrAfbr</i>	glucose	<i>p</i> -coumaroylptyramine	94.7 mg/L	



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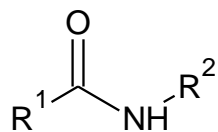
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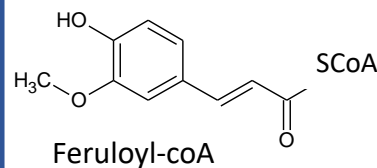
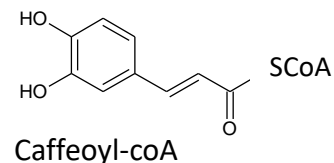
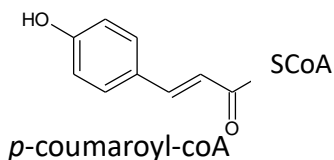
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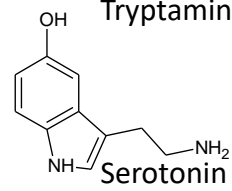
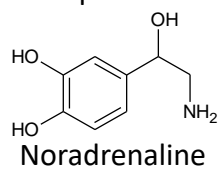
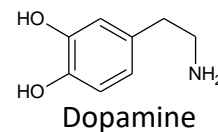
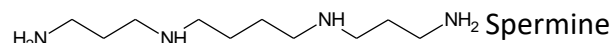
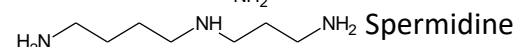
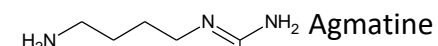
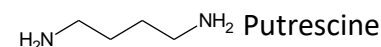
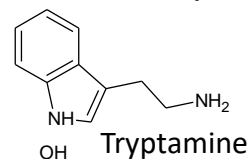
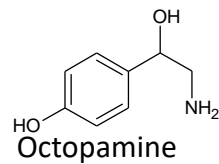
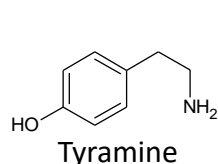
## Phenolamides



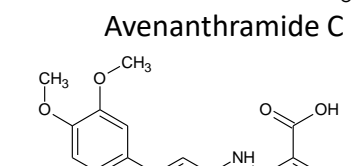
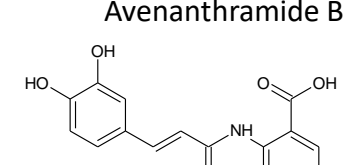
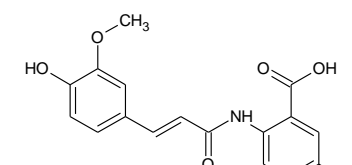
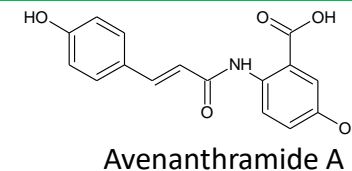
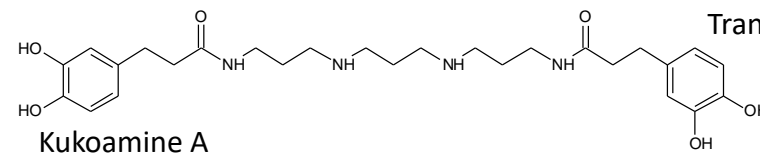
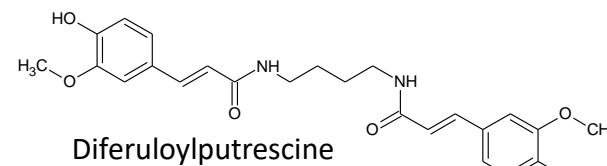
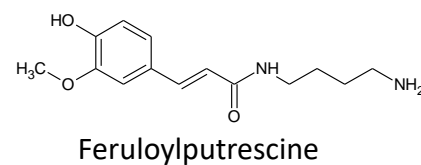
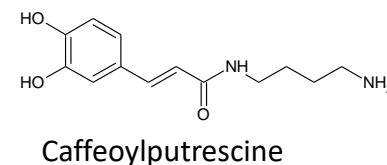
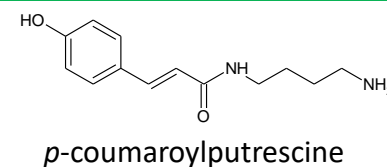
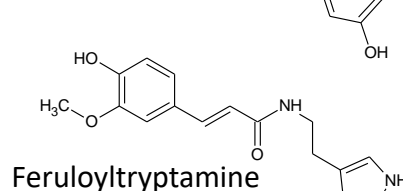
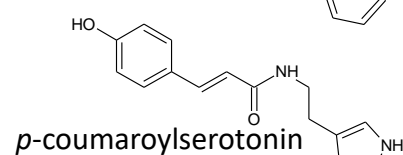
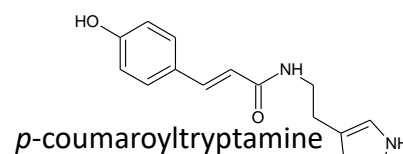
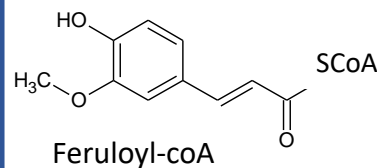
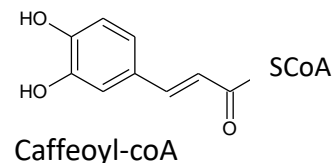
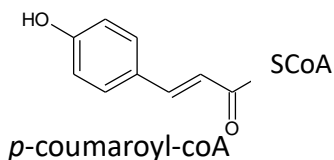
### Phenolic acids (R<sup>1</sup>)

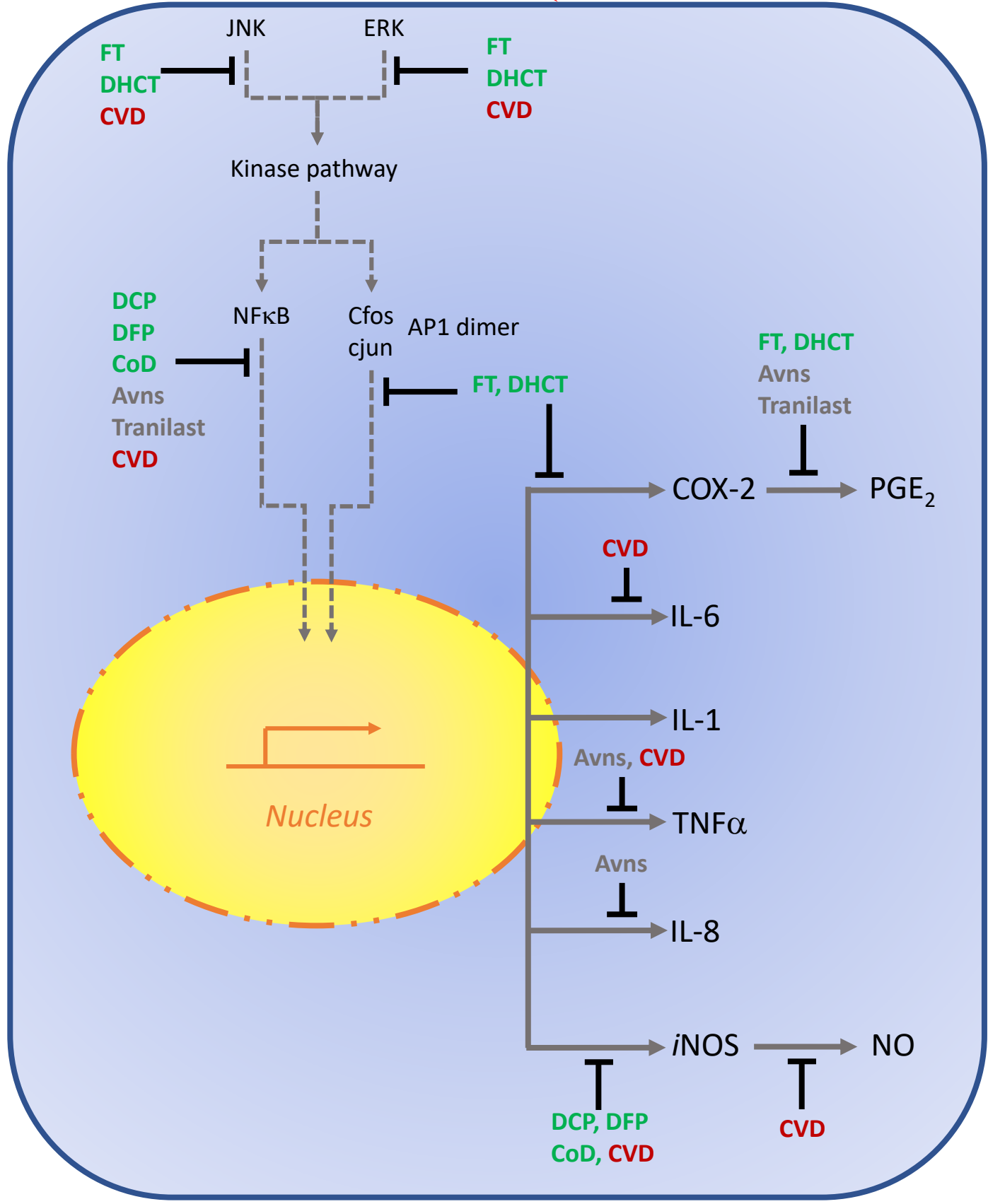


### Mono-/Poly-Amines (R<sup>2</sup>)



### Phenolic acids (R<sup>1</sup>)

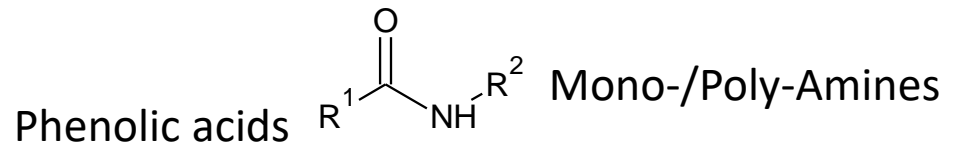








## Phenolamides



**Hundreds of structures**

