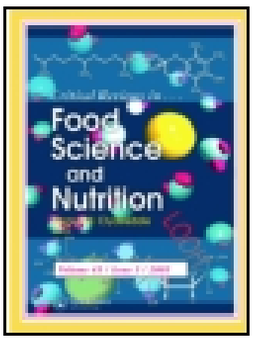

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REVIEW

Tyramine-derived hydroxycinnamic acid amides in plant foods: sources, synthesis, health effects and potential applications in food industry

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ABSTRACT

Tyramine-derived hydroxycinnamic acid amines (HCAAT) are naturally occurring group of secondary metabolites present in various plant genera, such as *Allium, Cannabis, Lycium, Polyganotum and Solanum*. It belongs to the neutral, water-insoluble compounds and plays a role in plant growth, development and defence mechanism. The past two decades have seen a shift in the study of HCAAT from its role in plants to its potent biological activities. This review highlights the sources, roles in plants, biosynthetic pathways, metabolic engineering and chemical synthesis of HCAAT. The biological properties of HCAAT remain the focus in this paper, including antioxidant, anti-inflammatory, anti-cancer, anti-diabetic, anti-melanogenesis and neuroprotective properties. The effects of food processing and technology on HCAAT are also discussed. Given the current research gap, this review proposes future directions on the study of HCAAT, as well as its potential applications in food and pharmaceutical industry.

KEYWORDS

Food processing; health benefits; hydroxycinnamic acid amide; metabolic engineering; nutrition

Introduction

Hydroxycinnamic acid amides (HCAAs) are a naturally occurring, diverse class of secondary metabolites with presumptive roles in plant growth, development and senescence (Facchini, Hagel, and Zulak 2002; Macoy et al. 2015). It arises from the condensation reaction between CoA esters of hydroxycinnamic acids with aliphatic/di/poly- or aromatic mono- amine groups. Therefore, HCAAs can be broadly classified into basic and neutral groups (Figure 1). The basic group is hydrophilic and ionizable, with aliphatic amine groups that include putrescine and spermidine. The neutral group is characterized by the absence of free amino group and its water-insoluble nature, possessing aromatic amines, such as tyramine, octopamine and tryptamine.

Accumulation of HCAAs was reported as a response to abiotic/biotic stress, wounding, fungal or pathogen attack in several plant species (Facchini, Hagel, and Zulak 2002). In addition to its role in plants, past in vivo and in vitro studies revealed potent antioxidant, anti-diabetic, anti-inflammatory, anti-melanogenic and cytotoxic properties of HCAAs. Due to its low content in plants, research investigating its potential use in food or pharmaceutical industry is relatively limited. However, increasing studies have sought to mass-produce HCAAs through metabolic engineering and chemical synthesis.

The focus of this review is on a subgroup of HCAAs which is derived from tyramine (HCAAT) biosynthesis in a variety of plant species (Figure 2). Although there are other subgroups of HCAAs which are derived from putrescine, spermidine or tryptamine (Figure 1), HCAAT are among the most studied HCAAs for its important role in plant foods and biological activities, as evident by past studies involving chemical assays, cell cultures and animal models. Researchers have extensively studied HCAAT in plants, including feruloyltyramine (FT), coumaroyltyramine (COT), caffeoyltyramine (CAT), cinammoyltyramine (CIT) and sinapoyltyramine (SIT) (Figure 2). Additionally, feruloyloctopamine (FO) and coumaroyloctopamine (COO) are also included as octopamine is derived from tyramine in the general phenylpropanoid pathway. These compounds occur in *trans* or the less common *cis* arrangement with different chemical properties. In addition, this review highlights both bioengineering and chemical approaches to synthesize HCAAT on a larger scale. Although scarce, this paper summarizes the effects of food processing methods and technologies on HCAAs, further justifies the need for additional research on its applications in the food and pharmaceutical industry.

Identification and concentration of HCAAT in different plant species and plant parts

HCAAT have been identified in numerous plant genus including *Allium, Cannabis, Lycium, Polyganotum and Solanum*. Other less frequently studied HCAAT, such as feruloyl-methoxytyramine and dihydro-feruloylmethoxytyramine, have been isolated from *Isodon excisus* and *Synsepalum dulcificum*, respectively (Lee et al. 2001; Wang et al., 2011).

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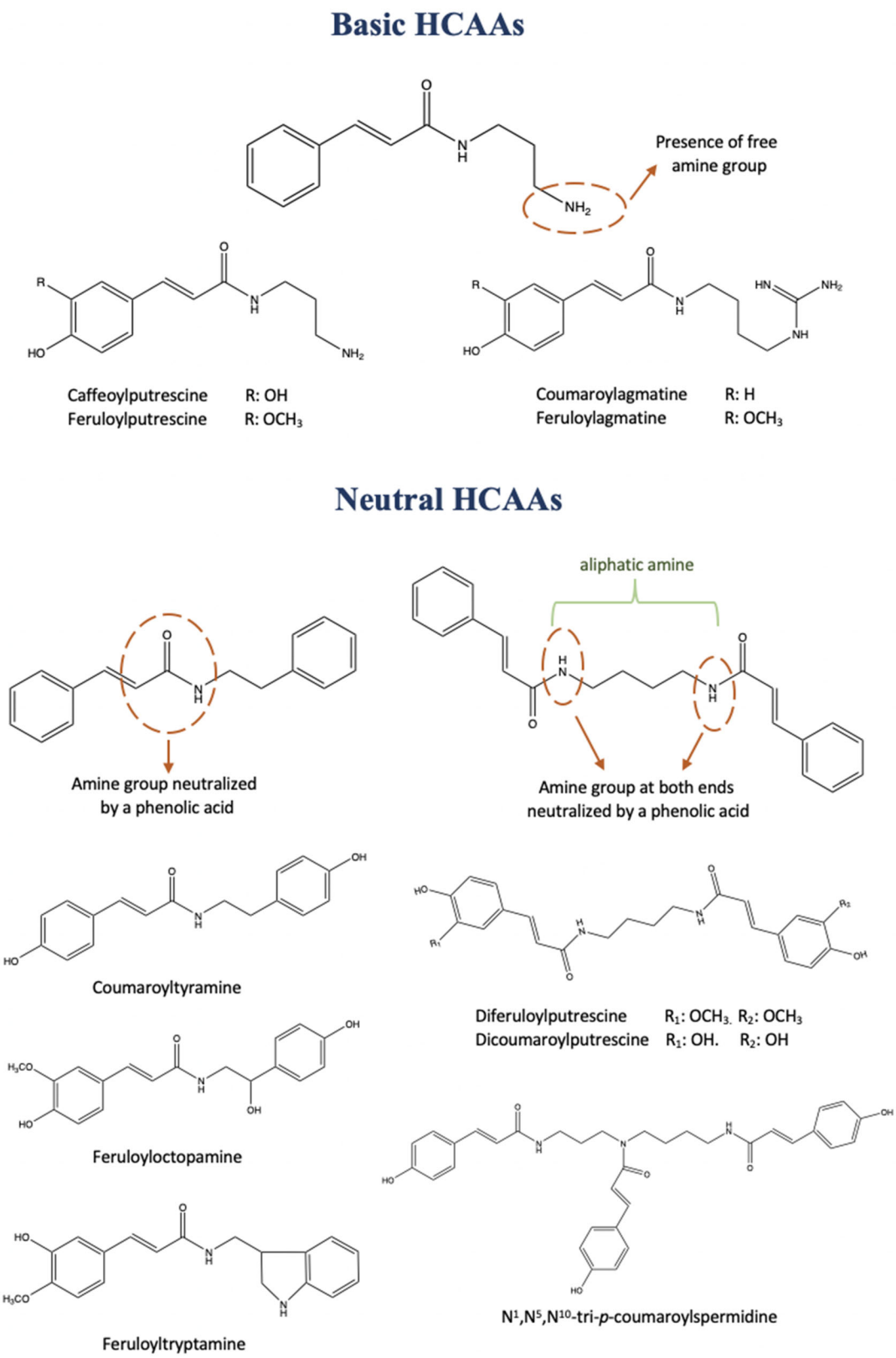

Figure 1. General classification of hydroxycinnamic acid amides.

Despite the extensive literature on HCAAT identification, there are fewer studies on its quantification due to the limited availability of standards (Table 1). Yamamoto et al. (1991) determined the content of *trans*-COT and *trans*-FT in plants (*Cannabis sativa* L.) for the first time with the aid of synthesized standards. They recorded higher content of HCAAT in seeds compared to other parts of the plant. However, while seeds and leaves were higher in *trans*-FT, *trans*-COT was the dominant HCAAT in roots. It should be noted that this quantification study was carried out around the same time as the discovery of *trans*-CAT in *C. sativa* (Sakakibara et al. 1992). A more recent study of *C. sativa* seeds revealed *trans*-

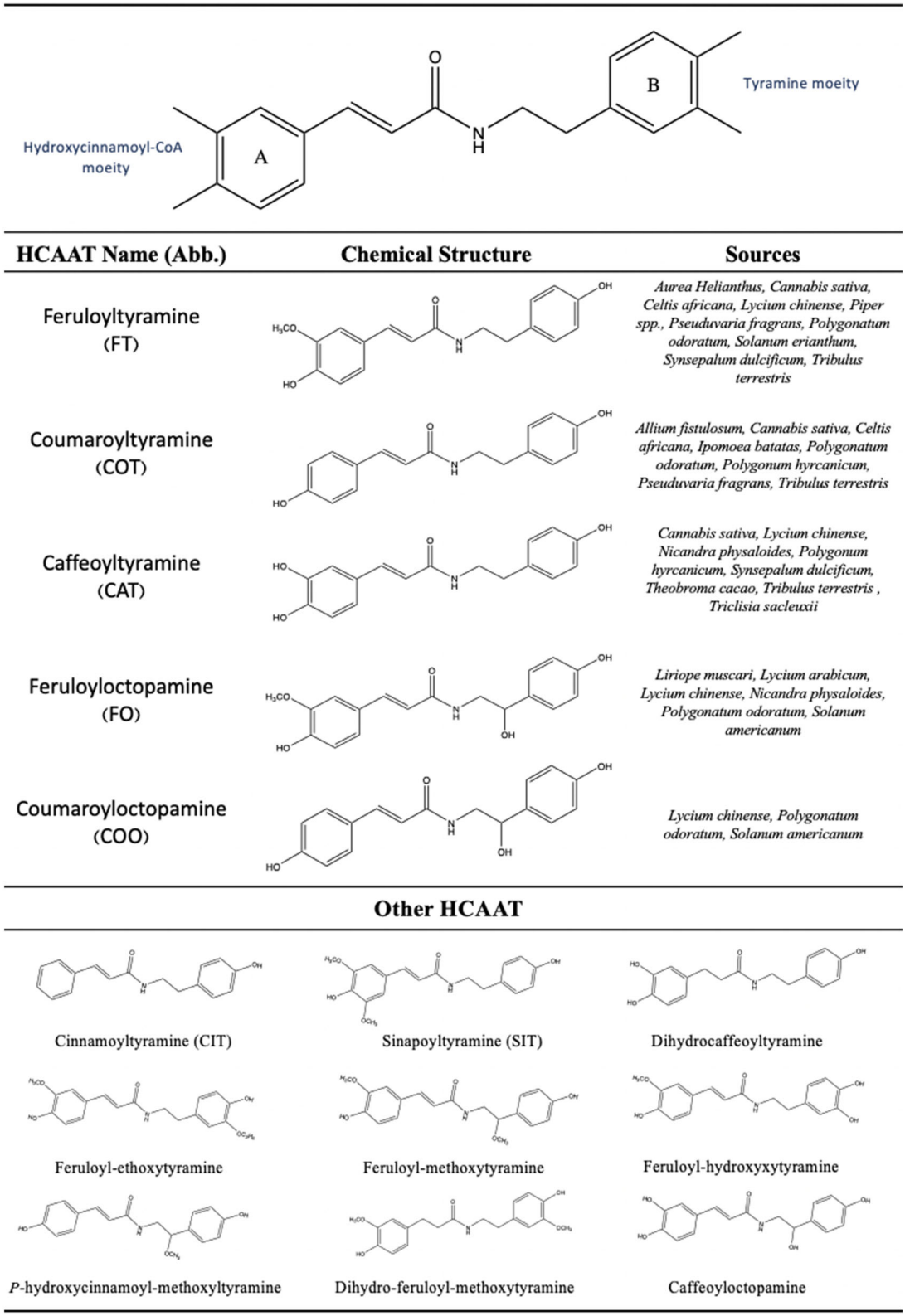

Figure 2. The core skeleton of HCAAT (top), common HCAAT and its sources (middle) and other less common HCAAT (bottom).

CAT as the most abundant HCAAT, followed by *trans*-FT, *trans*-COT and *trans*-CAO (Zhou et al. 2018). In *Lycium barbarum*, leaves possess the highest overall concentration of HCAAT than fruits or root barks, which could be due to the accumulation of *N*-*trans*-feruloyl-3-methoxytyramine as the dominant HCAAT (Wang et al. 2018; Wang, Suh, et al. 2017). Sun et al. (2015) assessed 17 root batches of *Solanum melongena* from nine different locations in China and reported a wide variation in their HCAAT content (Table 1). Moreover, Ly et al. (2008) reported the highest *trans*-CAT and *trans*-FT content in green onion after investigating several common food vegetables, such as cherry tomato, tomato

Table 1. Sources and content of HCAAT in plants from selected studies.

Species	Plant part	HCAAT content	Reference
Cannabis sativa L.	Leaves	N-trans-coumaroyltyramine: 2 μg/g N-trans-feruloyltyramine: 4 μg/g	Yamamoto et al. (1991)
	Roots	N-trans-coumaroyltyramine: 5 μg/g N-trans-feruloyltyramine: 2.6 μg/g	
	Seeds	N-trans-coumaroyltyramine: 7.5 μg/g N-trans-feruloyltyramine: 124 μg/g	
Allium fistulosum (green onion)	Whole edible parts	caffeoyltyramine: 13.85 ± 1.23 μg/g feruloyltyramine: 1.99 ± 0.15 μg/g	Ly et al. (2008)
Capsicum annuum (hot pepper)		feruloyltyramine: 1.26 ± 0.23 μg/g	
Solanum lycopersicum (cherry tomato)		caffeoyltyramine: 2.76 ± 0.57 μg/g	
Solanum lycopersicum (tomato)		caffeoyltyramine: 1.47 ± 0.80 μg/g	
Solanum melongena L. (eggplant)	Roots	N-trans-coumaroyloctopamine: 56.27 – 582.90 μg/g N-trans-feruloyloctopamine: 83.93 – 517.52 μg/g N-trans-sinapoyloctopamine: 11.70 – 64.09 μg/g N-trans-coumaroyltyramine: 83.24 – 535.51 μg/g N-trans-feruloyltyramine: 99.01 – 477.46 μg/g	Sun et al. (2015)
Lycium barbarum (wolfberry)	Fruits	N-trans-caffeoyltyramine: 0.24 μg/g N-trans-feruloyltyramine: 11.11 μg/g N-trans-feruloyl-3-methoxytyramine: 0.63 μg/g	Wang, Suh, et al. (2017)
Lycium barbarum (wolfberry)	Leaves	N-trans-caffeoyltyramine: 2.14 μg/g N-trans-feruloyltyramine: 20.76 μg/g N-trans-feruloyl-3-methoxytyramine: 42.2 μg/g N-3,4-dihydroxyhydrocinnamoyl tyramine: 1.7 μg/g	Wanget al. (2018)
	Root barks	N-trans-caffeoyltyramine: 26.44 μg/g N-trans-feruloyltyramine: 10.6 μg/g N-trans-feruloyl-3-methoxytyramine: 5.39 μg/g N-3,4-dihydroxyhydrocinnamoyl tyramine: 4,864.0 ± 74.9	
Cannabis sativa L. (Hemp)	Seeds	N-trans-caffeoyloctopamine: 8,040 μg/g N-trans-caffeoyltyramine: 25,080 μg/g N-trans-coumaroyltyramine: 10,530 μg/g N-trans-feruloyltyramine:15,170 μg/g	Zhou et al. (2018)

and hot pepper. These studies suggest that the content of HCAAT vary across species, plant parts and geographical location.

Biosynthesis and metabolic pathway of HCAAT

Both aromatic amino acids (AAA) of phenylalanine and tyrosine originate from the Shikimate pathway (Parthasarathy et al. 2018). The Shikimate pathway occurs in plants, fungi and bacteria, but not in animals. Briefly, this pathway includes condensation of erythrose 4-phosphate and phosphoenolpyruvate which leads to formation of 3-deoxy-D-arabino-heptulosonate-7-phosphate. Subsequent cascade of enzymatic reactions results in the synthesis of intermediates shikimate and chorismate. Chorismate undergoes conversion to prephenate, followed by an aminotransferase reaction into arogenate, the final branching point. Depending on the enzyme, generation of AAA from arogenate is facilitated by arogenate dehydrogenases of lyase-type for phenylalanine and oxidoreductase-type for tyrosine.

The general phenylpropanoid pathway itself is initiated by deamination of phenylalanine into trans-cinnamic acid through the action of phenylalanine ammonia-lyase (PAL) (Facchini, Hagel, and Zulak 2002) (Figure 3). Cinnamate 4-hydroxylase (C4H) facilitates the conversion of trans-cinnamic acid into p-coumaric acid. At this stage, p-coumaric acid may undergo hydroxylation into caffeic acid, and subsequently being converted into ferulic acid by caffeic-acid/5-hydroxyferulic acid O-methyltransferase (COMT). This is succeeded by esterification of these hydroxycinnamic acids by 4-(hydroxy)cinnamoyl-CoA ligase (4CL) into hydroxycinnamoyl-CoA esters, such as p-coumaroyl CoA, caffeoyl CoA and feruloyl CoA.

On the other side of the pathway, tyrosine decarboxylase (TYDC) facilitates the conversion of tyrosine into tyramine (Figure 3). Tyramine may be further converted to octopamine by tyramine β-hydroxylase (TβH). The final critical step is the condensation reaction of phenetylamines (tyramine, octopamine) and hydrocinnamoyl-CoA esters into respective HCAAT forms, most commonly FT and COT. This process is catalyzed by hydroxycinnamoyl-CoA:tyramine N-(hydroxycinnamoyl)transferase (THT), an enzyme that has been identified in several plants, such as tomato and tobacco (Yu and Facchini 1999).

THT appears to exhibit varying substrate specificity across different plants (Back et al. 2001). Pepper and potato THT favors tyramine as acyl acceptor with cinnamoyl-CoA as the acyl donor. In contrast, feruloyl-CoA is the preferred acyl donor by THT in maize and tobacco. Similarly, Yu and Facchini (1999) confirmed tyramine and feruloyl-CoA as the most suitable substrate for THT action in opium poppy, and the THT action is pH dependent. Moreover, caffeoyl-CoA exhibited poor specificity properties with opium poppy and tobacco THT, but the opposite finding was observed in potato THT.

The role of HCAAT in plant development, safety and defence

The importance of HCAAT as a growth regulator has been discussed by several past reviews (Facchini, Hagel, and Zulak 2002; Macoy et al. 2015). HCAAT can bind and form

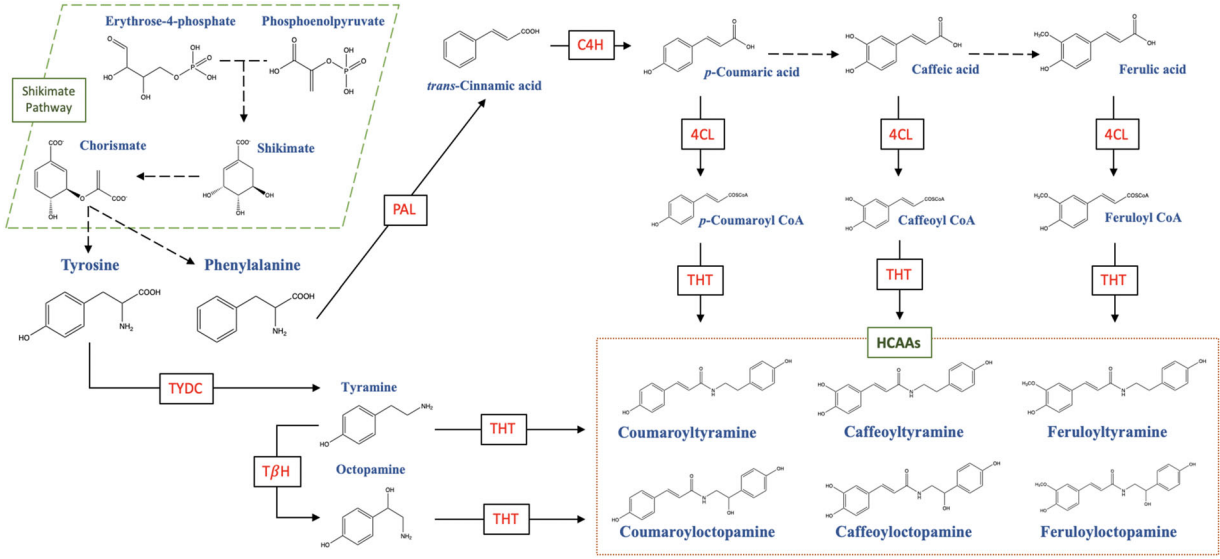

Figure 3. Biosynthetic pathway of HCAAT in plants. PAL: phenylalanine ammonia-lyase; C4H: cinnamate 4-hydroxylase; 4CL: 4-(hydroxy)cinnamoyl-CoA ligase; TYDC: tyrosine decarboxylase; THT: hydroxycinnamoyl-CoA:tyramine N-(hydroxycinnamoyl)transferase; TβH: tyramine β-hydroxylase.

dimers with cell wall components, including lignin and polysaccharides. This process increases the rigidity of cell wall, delay cell elongation and stem growth, and may strengthen the cell wall's resistance to physical, enzymatic or pathogenic attack (i.e. physical wounding or penetration, viral and fungal infection). von Röpenack, Parr & Schulze-Lefert (1998) indicated that the reduced degradation by fungal enzymes in barley's cell wall might be due to cross-linking of HCAAs. There is another possible role of HCAAs as a nitrogen sink, hence the capacity to supply additional amines required for cell division during plant growth. In opium poppy, the activity of THT, the main facilitator for HCAAT synthesis, increased with growth of seedlings (Yu and Facchini 1999). Additionally, there was less amount of THT polypeptides in mature xylem vessels than in developing counterparts. THT polypeptides were also found in anthers, ovule nucellus and the deeper layer of the seed coat. This implies on HCAAT's possible role in strengthening the cell walls of reproductive tissues.

Tyramine derived HCAAs appears to be involved in flower development, though the detailed molecular mechanism has yet to be explained. Early studies by Martin-Tanguy (1985) suggested the ability to distinguish floral organs based on the dominant amide profiles: neutral HCAAs, including COT and dicoumaroylputrescine/spermidine, in male reproductive organs, and basic HCAAs in female organs. Kang et al. (2006) reported a trend of increasing CAT and FT content from floral bud to pre-anthesis (before full opening) stage in pepper (*Capsicum annuum*) flowers. Despite significantly higher THT activity in stem and root, nearly all of HCAAT resided in flower, suggesting a likely migration of amine conjugates to concentrate to develop a particular plant part.

Accumulation of HCAAT in plants may act as a safety net to maintain parent compounds, such as tyramine, below toxic or inhibitory levels. Kim et al. (2011) showed that high levels of tyramine from overexpression of tyrosine decarboxylase (TYDC) gene inhibited cell mitosis during leaf development, thus resulting in dwarfed rice plants. Supplementation of tyramine led to the formation of black oxidation products in tobacco callus tissue cultures (Negrel, Javelle, and Paynot 1993). Under the presence of the oxidation agent tyrosinase, FT or COT displayed no toxic effect in cytokinin-treated medium. It appears that THT-catalyzed conjugation of hydroxycinnamic acids and amines may reduce the toxicity of tyramine by competing with formation of toxic quinones.

Fewer studies have supported the view of HCAAT as means of plant defence mechanism. Guillet and De Luca (2005) revealed a localized accumulation of COT and FT around the wounds of TYDC-expressed tobacco leaves. Similarly, physical wounding led to ten times increase in FT and COT in tomato leaves (Pearce et al. 1998). This effect was further intensified by supplementation of a plant defence elicitor chitosan. Nevertheless, accumulation of FT post-wounding was not apparent in other *Solanaceae* plants (pepper, nightshade), suggesting that even in the same family, the response to physical wounding differs between species.

Besides physical wounding, HCAAT provides a protection for plants against pathogenic invasion. Infection of tomato plants with tomato spotted wilt virus and citrus exocortis viroid intensified the accumulation of FT and COT (López-Gresa et al. 2016). Synthesis of these HCAAT, however, seems to favor varieties with higher risk of developing severe viral symptoms. The same lead author also reported the accumulation of *trans*-COO and *trans*-FO in tomato leaves after infection by bacterial pathogen *Pseudomonas syringae* (López-Gresa et al. 2011). This view supported earlier works by von Roepenack-Lahaye et al. (2003) and Zacarés et al. (2007), in which the response to bacterial pathogen in tomato plants was linked to HCAAs derived from tyrosine-related amines such as tyramine, octopamine, dopamine and noradrenaline.

Previous study showed that FT and COT from Persian leek (*Allium ampeloprasum*) significantly inhibited the growth of the pathogenic fungus *Botrytis cinerea* compared to control (Sadeghi et al. 2013). Though only FT displayed inhibition against other fungus *Aspergillus niger* and

Table 2. Selected studies on synthetic production of HCAAT.

HCAAT products	Catalyst/facilitator	Notes	References
Metabolic engineering			
N-p-cis-Coumaroyltyramine N-cis-Feruloyltyramine	THT gene from Nicotiana tabacum (tobacco) and TYDC gene from Papaver somniferum (opium poppy)	Higher accumulation of HCAAT in transgenic tobacco leaves after wounding	Hagel &Facchini (2005)
N-p-Coumaroyltyramine N-Feruloyltyramine	THT gene from Capsicum annuum	Significantly higher HCAAT content in transgenic shoots of rice (Oryza sativa).	Lee et al. (2007)
N-p-trans-Coumaroyltyramine N-trans-Feruloyltyramine	Binary vector pK2GW7,0:SHT T-DNA (SHT gene) from pepper	Significantly higher production of HCAAT in transgenic tomato (Lycopersicon esculentum L.) tissues compared to wildtype.	Kang, Lee, et al. (2009)
N-p-cis-Coumaroyltyramine N-cis-Feruloyltyramine N-cis- Caffeoyltyramine	Two, 4CL and THT – encoding, genes from Arabidopsis thaliana and pepper, respectively	Maximum production at 188, 175 and 31 mg/L, respectively, in Escherichia coli.	Kang, Lee, et al. (2009)
N-p-trans-Coumaroyltyramine	Four genes: 4CL from Oryza sativa, THT from Capsicum annuum, TDC from Papaver somniferum and TAL from Saccharothrix espanaensis	Maximum production at 495.4 mg/L in Escherichia coli.	Sim et al. (2015)
Chemical synthesis			
N-trans-Feruloyltyramine N-trans-Cinnamoyltyramine N-p-trans-Coumaroyltyramine N-trans- Caffeoyltyramine	Isobutylchlorocarbonate, THF and triethylamine.	Acetylation of respective acids pre-reaction. Yields of 54, 77, 54, 33%, respectively.	Tseng et al. (1992)
N-p-trans-Coumaroyltyramine	DIC, dimethylformide (DMF)	Conversion of cinnamic acid into symmetrical anhydride, before reaction with amine. Yield of 55%.	Park and Schoene (2002)
N-trans-Feruloyltyramine	Hydrazine monohydrate.	Condensation involving acetylated feruloyl chloride. Yield of 94%.	Nomura et al. (2003)
N-trans-Caffeoyltyramine N-trans-Sinapoyltyramine N-p-trans-Coumaroyltyramine N-trans-Feruloyltyramine	THF, N-hydroxysuccinimide, DCC.	Multiple steps, involved acidification (pH 2) before extraction. Yields of 14, 63, 53, 54%, respectively.	Pedersen, Steffensen, and Christophersen (2010)
N-trans-Cinnamoyltyramine N-trans-Feruloyltyramine N-trans-Caffeoyltyramine	DCC, N,N-dimethylaminopyridine (DMAP) and dry dichloromethane.	First step included transforming CA into phenethylamine forms, before conversion to HCAAT at low pH. Yields of 62, 57, 85%, respectively.	Yang, Song, and Liu (2011)
N-trans-Feruloyltyramine	Lipase: Novozyme 435, Lipozyme RM IM, Lipozyme TL IM, Flavourzyme 500MG, Candida rugosa lipase and Lipase Acidic.	One-step reaction. Lipozyme TL IM resulted in highest yield of 93.5%.	Alrub et al. (2012)
N-trans-Feruloyltyramine	Lipase (Lipozyme TL IM)	Response surface methodology. Maximum experimental yield of 96.3%.	Basri et al. (2014)

Penicillium italicum at the lowest concentration, it is likely that the presence of methoxy group in FT enhances antifungal activity. On the contrary, McLusky et al. (1999) did not detect direct antifungal activity by FT, COT or feruloylmethoxytyramine in onion epidermal cells, despite the accumulation of these HCAAT at the penetration site by *Botrytis allii*. The team proposed that these HCAAT act as precursors for peroxidase-catalyzed cross linking with cell wall components, thus reinforcing the strength of cell wall against physical penetration. Furthermore, *trans*-FT and *trans*-CAT isolated from *Xylopia aethiopica* significantly deterred feeding by termites at the concentration above 7500 ppm (Lajide, Escoubas, and Mizutani 1995). Replacement of hydroxyl group with methoxy group in HCAAT seems to increase anti-feedant activity on termites.

Bioengineered synthesis of HCAAT

The participation of HCAAT in plant growth, development and protection has been discussed above. However, HCAAT often occur in very low quantities. Several research teams have attempted genetic modification along the metabolic pathway to elevate the production of HCAAT (Table 2). The most common approach is to target THT expression through agrobacterium-mediated gene transfer from one plant to another host plant. Introducing overexpressed THT transgene from *Capsicum annuum* led to increased synthesis of FT and COT in young leaves of rice (Lee et al. 2007). This increase was proportional to the dose (0-20 mM) of external tyramine treatment. Contrary to a tobacco study by Negrel, Javelle, and Paynot (1993), toxic symptoms were absent in tyramine-treated rice plants. However, rice seedlings began to show stunted growth at tyramine dose of 5 mM. This may indicate the inability of HCAAT conjugation to suppress inhibition effect from excessive tyramine pool at a certain point, or that there is a direct inhibitory effect of HCAAT on seedling growth.

Rather than external treatment of tyramine, Hagel and Facchini (2005) constructed a transgenic tobacco plant with overexpressed THT and TYDC gene from tobacco and opium poppy, respectively. Higher accumulation of FT and COT (total sum of 0.10 versus 0.03 µmol/g dry weight at 12 hours after wounding) was found in wounded leaves of transgenic plant compared to wild type. Nevertheless, the

transgenes failed to effectively initiate the accumulation of cell wall bound HCAAT and the increase of THT/TYDC activity in roots. In addition to THT, another study transferred the gene encoding for serotonin N-hydroxycinnamoyltransferase, an enzyme theoretically involved in synthesis of serotonin-type HCAAs, such as feruloylserotonin and coumaroylserotonin, from pepper to tomato plants (Kang, Lee, et al. 2009). Even though serotonin N-hydroxycinnamoyltransferase displayed more affinity to serotonin, the richer tyramine content in tomato may have resulted in the higher production of HCAAT (FT and COT) compared to serotonin-HCAAs. These results highlight the complexity of metabolic engineering in plant hosts due to the possible interaction between multiple genes in the pathway and limited knowledge on factors from other substrates/metabolites.

Due to the apparent complexity of plant hosts, past studies have pursued an alternative synthesis of HCAAT in bacteria. The biology of *Escherichia coli* does not allow the production of hydrocinnamoyl-CoA esters. Therefore, Kang, Park, et al. (2009) introduced two, 4CL and THT – encoding genes from *Arabidopsis thaliana* and pepper, respectively. They reported an individual maximum production of *cis*-COT, *cis*-FT, *cis*-CAT at 188, 175 and 31 mg/L, respectively. Comparably high production rates were observed when all substrates (tyramine, hydroxycinnamic acids) were provided simultaneously. Excluding *cis*-COT, a preferential accumulation of HCAAT in *E. coli* occurred extracellularly in the medium fraction. Similarly, up to 495.4 mg/L of *trans*-COT was produced from *p*-coumaric acid in bioengineered *E. coli* expressing 4CL, THT, TYDC, TAL (tyrosine ammonia lyase) genes from various sources (Sim et al. 2015). Furthermore, engineering the Shikimate pathway in *E. coli* allowed the synthesis of 94.7 mg/L *trans*-COT from glucose (Sim et al. 2015). Production levels can be further maximized by optimizing incubation temperature and substrate concentration. In addition to HCAAT, metabolic engineering of *E. coli* has been employed for the synthesis of avenanthramide, serotonin and tryptamine-type HCAAs (Lee et al. 2017; Lee et al. 2018). This indicates the growing interest in bioengineered bacteria as a medium for mass production of plant secondary metabolites, such as HCAAT.

Chemical synthesis of HCAAT

Chemical synthesis of HCAAT as another means for mass production have been carried out by numerous researchers in the past (Table 2). The original starting material remains similar (tyramine and corresponding hydroxycinnamic acids), although the catalyst and solvents may be different, thus impacting the final yield. The first extensive record on the chemical synthesis of HCAAT was supplied by Tseng et al. (1992) with notable experimental features of: acetylation of cinnamic acids before reaction, solvents tetrahydrofuran and triethylamine. Results showed moderate yields for FT, CIT, COT, CAT at 54, 77, 54, and 33%, respectively. Park and Schoene (2002) took a different approach by firstly converting the cinnamic acid into symmetrical anhydride by 1,3-diisopropyl-carbodiimide (DIC), before reaction with tyramine. Additionally, the use of dicyclo-hexylcarbodiimide to facilitate condensation of tyramine and hydroxycinnamic acids was attempted (Pedersen, Steffensen, and Christophersen 2010; Yang, Song, and Liu 2011). However, no substantial increase in the yield for tyramine HCAAs was observed as compared to past findings.

One of the highest yields for FT, at 94%, was reported by Nomura et al. (2003), though the use of hydrazine monohydrate has raised concerns due to its toxicity. Driven by environmental-related reasons, Alrub et al. (2012) proposed the lipase-catalyzed chemical synthesis of FT with a yield of 93.5%. It is likely that lipase's flexibility to accept various substrates and its stability during chemical reaction have contributed to the high yield. Nevertheless, unlike previous studies, the use of HCL-protected tyramine was not suitable for the enzyme-catalyzed reaction. A follow-up response surface methodology study maximized the experimental yield at 96.3% (Basri et al. 2014). This is achieved by optimizing experimental conditions, including temperature of 43 °C over a span of 52 hours reaction time, substrate ratio for cinnamic acid: tyramine HCl of 6.2:1, and 260 mg of lipase. Hence, enzyme-catalyzed synthesis may provide a green alternative to produce HACCT with high yields.

Biological activities and potential health benefits of HCAAT

Antioxidant activities

Free radicals has been implicated for initiating oxidative stress and its involvement in cardiovascular diseases, diabetes mellitus and neurodegenerative disorders (Phaniendra, Jestadi, and Periyasamy 2015). Plant HCAAT has displayed strong ability to quench free radicals and reactive oxygen species (ROS) in several chemical assays. DPPH (2,2-diphenyl-1-picrylhydrazyl) spectrophotometric assay is frequently used to test antioxidant activities due to its simplicity and adequate sensitivity. Based on DPPH inhibition assay, *trans*-COT and *trans*-FT from *Lycium barbarum* fruits displayed stronger antioxidant activities than positive control BHA (butylated hydroxyanisole) (Gao et al. 2015). Both compounds also successfully inhibited lipid peroxidation in rat liver microsomes (Gao et al. 2015). No significant difference, however, was observed in inhibitory effect of *trans*-COT and *trans*-FT. This is in contrary to the *Liriope muscari* study by Li et al. (2012), who reported a considerably higher DPPH and ABTS (2,2′-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) inhibition by *trans*-FT and *trans*-FO, in comparison to *trans*-COT. They argued that the presence of methoxy group attached to the feruloyl moeity (Ring A) of the formers provides additional stability during inhibitory reaction, thus the superior antioxidant activity.

It appears that antioxidant activities may differ depending on the radical assay type. While FO posed a stronger effect on DPPH, FT showed more effective suppression on ABTS assay (Li et al. 2012). Zhang et al. (2013) confirmed that *trans*-CAT has the highest DPPH inhibition activity from all HCAAT tested from *Lycium chinense* extract. On the other hand, the same study reported the most potent nitroblue

tetrazolium superoxide radical inhibition by *cis*-FO from, stronger than its *trans* configuration and positive control Trolox. This suggests that some variations in antioxidant activities may due to the different plant source, chemical assays, isolation method and atomic arrangement.

Potent antioxidant capacities were also exhibited by HCAAT derived from chemical synthesis. Marinova et al. (2013) demonstrated stronger DPPH scavenging effect by synthesized CAT than caffeic acid. In addition, synthesized CAT displayed higher DPPH-radical inhibition than caffeic acid, FT, COT, and SIT (Park 2011b). High n_{app} indicates the ability of an antioxidant to supply more radical-trapping electrons, while low T_{EC50} shows the rapid action of phenols to trap radicals. Despite recording higher n_{app} value, parent compounds feruloyl and caffeoyl phenethylamine still displayed greater T_{EC50} and poorer DPPH/ABTS scavenging activity compared to CAT (Yang, Song, and Liu 2011). Therefore, it emphasizes the importance of ortho-dihydroxyl group attached to the Ring A (cinnamic acid-CoA moiety) of CAT to create a stable conjugation system with *resonance* structure.

Anti-diabetic properties

Diabetes mellitus has been described as the 'epidemic of the century', characterized by extremely high blood glucose (hyperglycaemic) levels from abnormal insulin secretion or resistance (Kharroubi and Darwish 2015). Alpha-glucosidase breaks down glycosidic bonds between carbohydrate units, which liberates glucose and induces postprandial hyperglycemia. Therefore, chemical assays for α-glucosidase inhibition have been one of the most studied methods as an initial step to identify potential anti-diabetic compounds.

The literature has indicated α-glucosidase inhibition effect of COT and several other HCAAT (Table 3). In a *Polygonatum odoratum* study, *trans*-COO, *trans*-COT, *trans*-FO and *trans*-FT have stronger α-glucosidase inhibitory effect than positive control deoxynojirimycin, with IC_{50} values of 2.3, 2.7, 198.6, and 234.1 µM, respectively (Zhou et al., 2015). These findings were in agreement to Panidthananon et al. (2018), who reported inferior α-glucosidase suppression by positive control acarbose as compared to *trans*-COT and *trans*-FT from *Pseuduvaria fragrans*. Unlike acarbose, COT and FT appear to display uncompetitive inhibition behavior on α-glucosidase. Uncompetitive inhibitors were claimed to be more effective than their competitive counterparts in in vivo testing, as their inhibition activity was minimally affected by increasing substrate concentration (Cornish-Bowden 1986). In addition to impeding α-glucosidase action, synthetic FT at 10 µM induced insulin release in rat pancreatic RIN-5F cells, thus contributing to lower blood glucose levels with minimum cytotoxic effects (Nomura et al. 2003).

Song et al. (2016) rearranged the structure of COT and subjected it to molecular docking trials, in an attempt to explain its potent α-glucosidase inhibition. Removal of hydroxyl group from Ring B (tyramine moiety) did not influence inhibition activity, though it lowered the number of available active sites to bind. However, removal of hydroxyl group from Ring A or double bond (α, β-unsaturated carbonyl group) of COT led to significant reduction in inhibitory capacity. Absence of the double bond decreased the average number of hydrogen bonds and extended plane-to-plane distance between Ring A and benzene ring of hydrophobic pocket Phe157. This suggests that the π- π interactions between the double bond is vital in ensuring the stability of COT as it binds to the hydrophobic pockets of the enzyme and inactivates it. Nevertheless, the same structural features may not explain other biological activities of HCAAT. trans-COT showed the highest α-glucosidase inhibition, but one of the weakest inhibitions on DPPH radical scavenging assay, as compared to other *Ipomoea batatas* compounds such as *trans*-FT and di/tri-coumaroylquinic acid (Zhang et al. 2016). The team also revealed that *cis* conformation and methyl group diminished the inhibition capacity of HCAAT.

Past in vitro chemical assays have indicated HCAAT as potent α-glucosidase inhibitors, but in vivo evidence is still scarce. Amaro et al. (2014) discovered that diet with the highest *trans*-FT concentration significantly lowered insulin resistance in C57/BL-6 mice compared to hypercaloric control diet and treatments with synthetic drugs (telmisartan + -pliogitazon). They suspected that this phenomenon may be due to *trans*-FT's role as a ligand for peroxisome proliferator's gamma receptor (PPAR-γ), of which its activation is linked to enhanced glucose metabolism and insulin sensitization. Aside from *trans*-FT, in vivo studies in animals have not been carried out for other HCAAT. Further in vivo studies involving animal or human participants are still required to test the efficacy of HCAAT, especially COT, on diabetic conditions.

Anti-inflammation and effect on inflammatory-related diseases

Inflammation serves as the body's immune response toward potentially damaging stimuli, including toxins, pathogens or impaired cells. Long-term, acute inflammatory response may substantially escalate the risk of asthma, cancers and neurodegenerative disorders (Chen et al. 2018). Lipolysaccharide (LPS) is a constituent of Gram-negative bacterial membrane that can trigger bioactive inflammatory mediators, such as nitric oxide. A common in vitro method to assess the anti-inflammatory property of a compound is through recording nitric oxide production in LPS-induced cell lines (Table 3). Ko, Ahn, and Oh (2015) detailed the significant NO inhibition on LPS-stimulated RAW 264.7 cells by *trans*-CAT from *Tribulus terrestris*, with the same effect as a positive control of NO synthase inhibitor NG-monomethyl-l-arginine L-NMMA. *trans*-CAT also showed the lowest concentration required to inhibit NO synthase in LPS-stimulated RAW 264.7 cells, compared to 15 other HCAAs modeled from wolfberry (Wang, Suh, et al. 2017). In contrast, *trans*-FT and N-*trans*-feruloyl 3-methoxytyramine only showed low to moderate activity in suppressing NO production. Moderate inhibition was also recorded by FT isolated from

Table 3. Selected studies on the biological activities of HCAAT and its potential health benefits.

Tested HCAAT	Source	Study type and brief method	Comments	Reference
Anti-diabetic				
N-trans-feruloyltyramine	Smilax aristolochiifolia roots	In vivo: C57/BL-6 mice	Significantly lower insulin resistance in HCAAT-rich extract than control.	Amaro et al. (2014)
N-trans-p-coumaroyloctopamine N-trans-p-coumaroyltyramine N-trans-feruloyloctopamine N-trans-feruloyltyramine	Polygonatum odoratum rhizomes	In vitro: a-glucosidase enzyme from Saccharomyces cerevisiae	Higher inhibition compared to positive control.	Zhou et al. (2015)
N-trans-coumaroyltyramine N-trans-caffeoyltyramine N-trans-feruloyltyramine	Fruits of Tribulus terrestris	In vitro: yeast a-glucosidase enzyme	Higher inhibition compared to positive control. Includes kinetic and molecular docking analysis.	Song et al. (2016)
Anti-inflammation				
N-trans-p-coumaroyltyramine N-trans-feruloyltyramine N-trans-caffeoyltyramine	Aerial parts of Celtis africana	In vivo: Wistar rats	Inhibition of edema in carrageenan-induced rat paws.	Al-Taweel et al. (2012)
N-trans-feruloyltyramine	Solanum erianthum roots	In vitro: RAW264.7 murine macrophage cell lines	Moderate nitric oxide inhibition in LPS-induced cells.	Chen et al. (2013)
N-trans-caffeoyltyramine,	Chemical synthesis	In vitro: RAW264.7 murine macrophage cell lines	Significant inhibition of nitric oxide production in LPS-induced cells.	Wang, Wang, et al. (2017)
Anti-melanogenesis				
N-trans-caffeoyltyramine, N-dihydrocaffeoyltyramine N-trans-dihydro-p-hydroxycinnamoyltyramine	Chemical synthesis	In vitro: human melanocytes In vivo: tolerance on rats and rabbits	Suppression of tyrosinase, thus melanin biosynthesis.	Okombi et al. (2006)
N-trans-Feruloyltyramine	Bark of Euphorbia cupularis	In vitro: Murine B16 melanoma cells	Inhibition of tyrosinase, thus melanin production.	Efdi et al. (2007)
N-trans-Feruloyltyramine	Aurea Helianthus stem	In vitro: B16 melanoma cells	Suppression of tyrosinase, MITF, TRP-1, TRP-2 expression and melanin synthesis.	Kim et al. (2018)
Cytotoxic and anti-cancer				
N-trans-p-coumaroyltyramine	Chemical synthesis	In vitro: Human U937 and Jurkat tumor cells	Inhibition of protein tyrosine kinases and tumor cell growth.	Park and Schoene (2002)
N-trans-Feruloyltyramine	Corydallis pallida (whole)	In vitro: adenocarcinoma SNU-638 and fibrosarcoma HT-1080 cell lines	No effect	Kim et al. (2005)
Dihydro-caffeoyltyramine	Screening of Chinese medicine database	Molecular docking and interaction analysis	High potential as Co-chaperon p23, a tumor growth stimulant, inhibitor.	Dwivedi et al. (2018)
N-trans-Feruloyltyramine	Laba garlic	In vitro: Human hepatoma cells (HepG2) cells and Human normal hepatocyte cells (L02) cells In vivo: H22 tumor affected mice	Improved cell viability, of ROS-induced L02 cells. Inhibition of HepG2 growth. Reduction of tumor weight in mice.	Gao et al. (2019)
Metabolic syndrome				
N-trans-Feruloyltyramine	Smilax aristolochiifolia roots	In vivo: C57/BL-6 mice	FT-rich extract reduced triglyceride, weight and blood pressure.	Amaro et al. (2014)
Neuroprotective				
N-trans-caffeoyltyramine	Lycium chinense root barks	In vitro: PC12 rat adrenal gland cell lines	Cytoprotective effect against hydrogen peroxide-induced cell damages.	Olatunji, Chen, and Zhou (2017)
N-cis-feruloyltyramine N-trans-feruloyloctopamine N-trans-caffeoyltyramine	Fruits of Nicandra physaloides	In vitro: human SH-SY5Y neuroblastoma cells	Protection on cells from neurotoxin MPP+	Wang, Wang, Wang, et al. (2017)

roots of *Solanum erianthum* (Chen et al. 2013). Hence, the presence of methoxyl group might reduce the anti-inflammatory properties of HCAAT.

Cyclooxygenases (COX), including its isoforms COX-1 and COX-2, and Lipooxygenases (LOX) are involved in the production of inflammatory mediators, such as prostaglandins, and regulation of inflammatory diseases (Burnett et al. 2007). Park (2007) has ranked the COX-1 and COX-2 inhibitory activity of common HCAAT on platelets in a decreasing magnitude: CAT, FT, COT, and CIT. CAT blocks the expression of P-selectin, a transmembrane glycoprotein linked to platelet activation and platelet-endothelium/leukocyte binding, which leads to reduction in activity of COX and its prostaglandins thromboxane B2. On the other hand, *trans*-FT suppressed COX-2 by interfering with the activation protein 1 and c-Jun N-terminal kinase signaling

pathways (Jiang, Yu, and Wang 2015). Although CAT and FT possessed high COX inhibition activity, the same potent effect was not observed on LOX isoforms 5-LOX and 15-LOX (Park 2011a). This may suggest a more suitable application of HCAAT against COX-linked conditions such as cardiovascular diseases, rather than LOX-related asthma and autoimmune disorders.

In addition, dihydro-CAT from the root bark of *Lycium chinense* reversed the stimulating effect of phorbol 12-myristate 13-acetate on COX-2 activity and PG-E_2 release in RAW 264.7 cells (Han et al., 2010). Suppression of COX-2 by dihydro-CAT was accomplished by intercepting signal transduction pathways of mitogen activated protein kinases, thus silencing activator protein AP-1 and CCAAT/enhancer-binding protein C/EBP. It appears that the inhibitory action of dihydro-CAT on phorbol 12-myristate 13-acetate-challenged cells was not mediated by transcriptional factor nuclear factor kappa B (NF-κB), despite promoter construct experiments showing the direct effect of dihydro-CAT on NF-κB. These conclusions were incongruent to the research by Xie et al. (2014), who reported significant NF-κB inhibition by CAT from *Lycium chinense* root barks in cells induced by tumor nuclear factor α. The team linked this activity on the ortho-diphenol group and α,β-unsaturated carbonyl group, a critical part of the Michael addition acceptor structure. As a result, the inhibitory mechanism of HCAAT on transcriptional factors seems to differ by the presence of double bond carbonyl group and type of introduced stimuli.

Animal studies have been carried out to assess the anti-inflammatory properties of HCAAT. Kidney and adipose tissues of mice fed with FT-rich *Smilax aristolochiifolia* extract contained lower ratio of pro-inflammatory cytokines IL(interleukin)-1β, IL-6, tumor nuclear factor α and anti-inflammatory cytokines IL-10, as compared to control (Amaro et al. 2014). Al-Taweel et al. (2012) divided Wistar rats into five treatments (control, positive control, COT, FT, CAT) after injecting carrageenan to induce acute paw edema. They found inhibition of edema enlargement by COT, FT, CAT from *Celtis africana* by 48, 33, 26%, respectively, comparable to positive control diclofenic sodium at 58%. However, the exact mechanism of this inhibition in carrageenan-induced paw odema model is unclear. It is likely that HCAAT directly affects the NF-κB, toll-like receptor 4 and B cell leukemia/lymphoma 6 inflammatory pathways induced by carrageenan (Bignotto et al. 2009). Carrageenan edema has also been associated to generation of COX, leucocytes and platelet-activating factors in earlier phases; and reactive oxygen species at the later stages (Bhattacharyya et al. 2011). Therefore, antioxidant properties of HCAAT may contribute to the reduction of inflamed paw edema in mice model.

Cytotoxic and anti-cancer properties

Cancer, a diverse group of mutation-derived diseases, is one of leading causes of human death worldwide. Previous findings on the cytotoxic effect of HCAAT against in vitro cell lines have been conflicting (Table 3). Park and Schoene (2002) revealed *trans*-COT's cytotoxicity rate on human tumor U937 and Jurkat cell lines by around 58 and 60%, respectively, at a maximum concentration of 90 µM. COT was speculated to inhibit the activity of tyrosine kinase EFGR (epidermal growth factor receptor), a key mediator in cancer cell progression, in an apoptotic or programmed behavior. Likewise, the same researchers demonstrated *trans*-CAT's inhibitory action on the growth of U937 and Jurkat cells, which was superior to *trans*-FT, *trans*-CIT, and *trans*-SIT (Park and Schoene 2003). *Trans*-CAT activated apoptotic cell death at a faster rate compared to COT, as evident by the early induction of CPP32/Caspase-3 protease and DNA degradation.

The presence of α,β-unsaturated carbonyl group (double bond) is integral for HCAAT to exhibit potent anti-diabetic and anti-inflammatory properties, as described in the above Sections. However, it appears that the absence of this group does not discount the cytotoxic potential of CAT. Co-chaperon p23 protein is a principal component for heat shock protein 90 to initiate cascades of tumor growing and metastatic processes. Dihydro-CAT displayed the strongest binding to co-chaperon p23 protein out of 200 potential inhibitors screened from the Traditional Chinese Medicine database (Dwivedi et al. 2018). This was explained by selective hydrogen bonding and hydrophobic interactions formed between important active site residues of p23 (Ala-94, Lys-95, Thr-90) and dihydro-CAT. As a result, inactivation of p23 and its chaperoning action may induce apoptotic death of cancer cells.

Previous researches have detected the cytotoxic effects of FT on mouse hepatoma Hepa-lclc7 and human lung cancer SPC-A-1 cell lines (Jang et al., 2003; Wang et al. 2012). Basaiyye et al. (2018) proposed that *trans*-FT catalyzed both intrinsic and extrinsic apoptotic pathways in leukemic cells. FT initiated the intrinsic pathway by upregulating the expression of tumor-suppressing genes *TP53* and transcription factor nuclear factor of kappa light NFKB1. *In silico* analysis revealed *trans*-FT's capacity to extracellularly bind and activate tumor necrosis factor-1 TNFR-1, hence inducing a set of caspase activity that leads to chromatin condensation and DNA fragmentation commonly observed in apoptosis.

Unlike other HCAAT, FT exhibited selective cytotoxic properties in in vitro cancerous cell lines. *trans*-FT from laba garlic suppressed (IC_{50}: 194 µM) growth of human hepatoma HepG2 cells in a dose-dependent manner (Gao et al. 2019). Although the effect was weaker than positive control taxol (IC_{50}: 26 µM), no effect was observed on the viability of healthy hepatocyte L02 cells. At 320 µM, FT maintained a 90% survival rate of L02 cells exposed to hydrogen peroxide, with no significant effect on cell morphology and mitrochondrial integrity. Additionally, inhibition of H22 tumor growth in mice model by FT-rich fraction of laba garlic has a comparable effect to positive control cyclophophamide. These results highlight the potential application of FT in targeted cancer treatments and development of pharmaceutical products.

Several studies, however, failed to report potent cytotoxic properties of HCAAT on cancer lines. No cytotoxicity against human ovarian cancer OVCAR-3 cells was detected in *trans*-COT and *trans*-FT purified from *Solanum indicum* (Syu et al. 2001). *Trans*-FT and *trans*-methoxy-FT from *Corydallis pallida* were inactive on human stomach adenocarcinoma SNU-638 and fibrosarcoma HT-1080 cancer cell lines (Kim et al. 2005). In addition to the low-moderate cytotoxicity, Samita et al. (2017) reported lower cytotoxic effect by *trans*-CAT compared to *trans*-FT against human adenocarcinoma (HeLa), breast carcinoma (MCF-7) and human hepatocarcinoma (Hep3B) cell lines, which is in contrary to Park and Schoene (2003). Though the extent, by which the ortho dihydroxyl groups in CAT resulted in lower cytotoxic activity, remains uncertain. The diversity of cancer cell lines and its underlying genetic mutations may contribute to the discrepancies of these findings. Thus further in vivo studies are needed to prove the anti-cancer properties of HCAAT.

Skin health and anti-melanogenesis activity

Melanin plays a vital role in human skin color and protection. Nevertheless, over-accumulation of melanin may lead to hyperpigmentation, a skin condition characterized by acne scars, dark melasma patches and sunspots (Zolghadri et al. 2019). Tyrosinase and tyrosine-related proteins (TRP1/2) directly regulates melanin biosynthesis. Tyrosinase, in particular, triggers two prerequisite steps for synthesis of melanin: hydroxylation of L-tyrosine to 3,4-dihydroxy-L-phenylalanine (L-DOPA), and conversion of L-DOPA to *ortho*-quinone (Zolghadri et al. 2019).

Earlier in vitro cell trials have demonstrated tyrosine inhibition activities of FT and CAT (Table 3). Efdi et al. (2007) revealed a more potent (60%) inhibition of melanin production by *trans*-FT from *Euphorbia cupularis* than positive control kojic acid (20%) at 10 µM, without significantly affecting viability of murine B16 melanocytes. They suggested FT's role in restricting the expression of tyrosinase protein, instead of directly interfering with tyrosinase activity. This view was consistent with the research led by Kim et al. (2018), who reported that *trans*-FT from *Aurea helianthus* (AH) significantly inhibited the expression of tyrosinase, TRP-1, TRP-2 mRNA and protein in hormone-stimulated murine B16 melanocytes. Similarly, no cytotoxic effect on the melanoma cells was evident by *trans*-FT-rich AH extract at the concentrations of 0-500 µg/mL. In addition to melanin inhibition, *trans*-FT from stems of *Lycium chinense* considerably improved the release of procollagen type I peptide in murine macrophage RAW 264.7 cells in comparison to ascorbic acid (Gil, Jang, & Eom, 2017). This may indicate FT as a potential component of whitening or anti-aging skin products.

Development of products containing tyrosinase inhibitors, however, have been strictly regulated due to safety concerns in the past. Several researchers have recognized this issue and adopted human melanocyte cells to mimic the actual skin cell condition (Table 3). In human melanocytes obtained from abdominal plastic surgery, synthesized *trans*-CAT and *trans*-dihydro-CAT nearly recorded complete (94-100%) tyrosinase inhibition at 0.1 mM, which was higher than kojic acid (20%) and *trans*-FT (49%) (Okombi et al. 2006). A follow-up oral administration of these compounds on rats revealed no toxicity of these compounds at dose of 2 g/kg, although additional studies involving human participants are still required to test its safety and effectiveness. Contrary to the findings outlined before, tyrosinase suppression by *trans*-FT and *trans*-CAT from *Synsepalum dulcificum* stems was not significant in human melanoma A375.S2 cell lines (Wang et al. 2011). The group advised alternatively on the tyrosinase/melanin-inhibition action of *cis*-FT, although it displayed weaker DPPH radical scavenging activity than *trans*-FT. Thus, further investigation to assess the possibility of other anti-melanogenic HCAAT in *cis* arrangement is needed.

Aside from melanogenesis, in vivo mice study has shown HCAAT's potential to treat inflammatory-related skin condition atopic dermatitis. Synthesized *trans*-COT inhibited the increase in ear epidermal/dermal thickness and antibodies immunoglobulin E levels of AD-induced mice (Choi et al. 2019). In vitro T cells trial revealed that *trans*-COT regulated T-helper Th-1 and Th-2 immunological response, thus inhibiting the mRNA levels of inflammatory cytokines IL-4, IL-5, IL-13. It seems that the absence of hydroxy group from ring B of *trans*-COT further improved its amphiphilicity, thus its greater permeability into cell membranes and anti-atopic dermatitis effects.

Neuroprotective effect

Oxidative stress and generation of ROS have been linked to progression of several neurological disorders, such as Alzheimer's and Parkinson's disease. In vitro cell lines have revealed HCAAT's neuroprotective effect against oxidative stress (Table 3). Treatment of *trans*-CAT (40 µM) from *Cortex lycii* nearly reversed the changes induced by hydrogen peroxide (100 µM) in rats PC12 neural cell model, which includes reduced cell viability, increased lactate dehydrogenase and caspase-3 activity, accumulation of intracellular ROS and calcium ions (Olatunji, Chen, and Zhou 2017). *trans*-CAT also restored internal antioxidant enzyme (catalase, superoxide dismutase, glutathione) levels and the balance between pro-apoptosis Bax and anti-apoptosis Bcl-2 proteins, thus preventing mitochondrial impairment that may lead to neuron death. The activity of amyloid β-peptide (Aβ), a component of amyloid plaques, is associated with ROS generation, membrane lipid peroxidation and increased risk of Alzheimer's disease (Smith, Cappai, and Barnham 2007). Thangnipon et al. (2012) demonstrated *Polyalthia suberos* *trans*-FT's capacity to significantly improve the viability, reduced ROS, caspase-3 activity and Bax levels of Aβ-treated rat cortical neurons. Hence, the strong antioxidant and radical scavenging capacity of HCAAT may also be credited for its neuroprotective properties.

In comparison to several HCAAT from *Nicandra physaloides*, *cis*-FT, *trans*-FO and *trans*-CAT presented the highest

protection on human dopaminergic SH-SY5Y neuroblastoma cells induced by neurotoxin 1-methyl-4-phenylpyridiniumion (MPP+) (Wang, Wang, Wang, et al. 2017). This study provided several inferences regarding the structure-activity relationships of HCAAT: (1) the presence of methoxy or hydroxy group at *meta* position is crucial, (2) presence of methoxy group at *para* position may reduce the cytoprotective effect, and (3) *cis* double bond arrangement led to more potent neuroprotective effect than its *trans* counterpart. Besides regulating proteins involved in mitochondrial apoptosis pathway, *cis*-FT accelerated autophagy, a cell survival mechanism characterized by degrading and reusing cytoplasmic components, hence the potential therapeutic effect on Parkinson's Disease. Moreover, LPS-challenged mice fed with hempseed phenylpropanoid extract (highest concentration of *trans*-CAT) at 1-2 g/kg displayed enhanced learning ability and memory function, as shown by the longer time navigating the Morris water maze platform (Zhou et al. 2018). Morphological staining showed that the extract recovered the damage caused by LPS on nerve cells of hippocampal CA3 region. However, confirming the neuroprotective effect of HCAAT necessitates further trials using different animal model and biomarkers, before potential human study.

Other biological properties

Anti-bacterial and parasitic properties

In addition to the major biological activities discussed in the previous sections, HCAAT has displayed anti-microbial, anti-parasitic properties, potent metabolic syndrome management and strong interaction with human transport protein. Nevertheless, the evidence to support these activities is still very limited. *trans*-FT and *trans*-CAT from aerial parts of *Triclisia sacleuxii* showed more effective inhibition of *Staphylococcus aureus*, with minimum inhibitory concentration of 7.8 and 15.7 μg/ml, comparing to positive control tetracyline at 125 μg/ml (Samita et al. 2017). Both HCAAT also showed satisfactory inhibition against Gram-positive *Escherichia coli*, *Pseudomonas aeruginosa* and Gram-negative *S. epidermidis*. This indicates the possible application of HCAAT as food preservatives, although Meerungrueang and Panichayupakaranant (2015) found weak to absent activity of *trans*-FT from *Ficus foveolata* against *S. pyogenes* and *S. mitis*. *trans*-CAT, *trans*-COT and *trans*-FT displayed the highest toxicity against protozoan parasite *Trypanosoma brucei*, as compared to the compounds isolated from *Polygonum hyrcanicum*, such as *p*-coumaric acid, ferulic acid and cannabisin B (Moradi-Afrapoli et al. 2012). Infection by *Trypanosoma brucei* causes vector-transmitted human African trypanosomiasis (sleeping sickness), as typified by the disruption of the sleep-wake circadian rhythm cycle and sleep pattern fragmentation (Brun et al. 2010). Though the detailed mechanism remains to be elucidated, the anti-parasitic activities of these HCAAT seem to retain a degree of selectivity, as shown by the low-moderate cytotoxic effect against rat skeletal L6 myoblasts.

Metabolic syndrome

Consumption of *trans*-FT has the potential to reduce risk of metabolic syndrome conditions of obesity, hypertriglyceridemia and hypertension. Treatment of mice with FT-containing *S. aristolochiifolia* extract protected against excessive growth rate, reduction of body density and increased blood (systolic/diastolic) pressure induced by hypercaloric diet and angiotensin II (Amaro et al. 2014). Furthermore, diet with the highest *trans*-FT concentration significantly depleted serum triglycerides compared to positive control pioglitazone and telmisartan. As described previously, *trans*-FT contributes to activation of PPAR-γ, thus the improved regulation in lipid metabolism (Srivastava 2011). Another possibility is the role of *trans*-FT in downregulating expression of blood pressure regulator TNF-α, though a direct causal link has yet to be established (Amaro et al. 2014).

Interaction with human serum albumin

Human serum albumin (HSA) is the most abundant protein in human's circulatory system. It selectively interacts with various molecules, consequently affecting its bioavailability and pharmacological properties in the body (Zsila, Bikádi, and Simonyi 2003). As a result, it has clinical value as a carrier of drugs, oxygen and fusion proteins for treatment of blood loss, hemorrhage and internal organ injury (Fanali et al. 2012). Neelam et al. (2010) reported that HSA can bind to two molecules of *trans*-COT, with a binding affinity of 4.5×10^5 M^{-1}. This value was higher than common polyphenols resveratrol (1.64×10^5 M^{-1}) and quercetin (1.46×10^4 M^{-1}). The conformation of HSA increased in β-sheets and decreased in α-helix, with higher concentration of *trans*-COT and formation of COT-HSA complex. Based on molecular docking trials, the authors concluded that the COT-HSA interaction was mainly hydrophobic, with several hydrogen bonds to stabilize the molecule.

The binding properties of *trans*-CAT contrasts with *trans*-COT, of which only one molecule was able to bind to HSA (Ma et al. 2016). The CAT-HSA interaction was dictated by hydrogen bonds and van der Waals forces, with elevated α-helix content at higher *trans*-CAT concentration. However, both HCAAT bind to HSA's site I in subdomain IIA. This suggests that different HCAAT may interact with and affect HSA in a distinct manner. Understanding HCAAT-HSA interaction is essential to further comprehend HCAAT's transport, bioavailability and biological actions in the body.

Bioavailability of HCAAT and its effects on gut microbiota

There are limited studies on FT's bioavailability using in vivo rodent model. Park (2016) claimed an adequate absorption of FT in mice gut, with a peak plasma concentration (0.65 μmol/L) at 20 minutes over a 60-minute period after administering 10 μg/35 g body weight of FT. Xu et al. (2018) indicated that a large portion of *trans*-FT from *Datura metel* seeds underwent Phase II metabolism and can be hydroxylated by P450 enzymes in rats. Dehydrogenation and hydroxylation were the main metabolic reactions,

resulting in up to eight different metabolites, including glucuronide and sulfate conjugates, as detected in plasma, fecal and urine samples. It seems that the presence of methoxy group may positively affect the oral bioavailability of HCAAT.

Currently, there is a research gap on the in vivo effects of individual HCAAT on gut microbiota. Treatment of HCAAT-rich hempseed extract, however, led stability in growth of most beneficial *Bifidobacterium* and *Lactobacillus* spp. strains, and significantly higher growth for *L. plantarum* from 0.5-2.5 mg/ml (Frassinetti et al. 2020). On the other hand, the growth of several pathogenic strains, such as *E. coli, Salmonella typhimurium, and Staphylococcus aureus*, were markedly suppressed by hempseed extract at the same concentration range. The higher ratio of beneficial bacteria may promote a healthier gut microbiota by releasing bioactive compounds, preventing pathogen adhesion to intestinal mucosa and competition with pathogenic strains for nutrients (Frassinetti et al. 2020). Therefore, the selective antimicrobial activity of HCAAT containing extract necessitates further in vivo testing on the effects of HCAAT on the gut microbiota.

Effect of food processing and technology on HCAAT and their potential application in food and pharmaceutical industry

There are very limited reports on the effect of food processing and food matrix on HCAAT. Long term storage for 36 months, in the dark and at room temperature, reduced overall *trans*-COT and *trans*-FT content of *C. sativa* seeds (Matsunaga et al. 1997). Although the reason was unclear, 12-months storage increased the *trans*-FT content, and *trans*-COT remained stable for the last 24 months of the storage period, only in Minamioshihara strain of *C. sativa*. However, in CBDA strain, content of both *trans*-COT and *trans*-FT decreased at the end of the storage period. This research group also observed isomerization of *trans*-FT into *cis*-FT after UV irradiation. This phenomenon was supported by Pedersen, Steffensen & Christophersen (2010), who indicated the presence of *cis*-FT as a possible artifact of the UV isolation procedure. UV appears to weaken the amide group attached to the benzene ring, thus the double bond is shifted upfield to protect the olefinic (double-bonded hydrocarbon) protons.

The effect of different drying processes on HCAAT have been assessed by previous studies. Drying reduces the water activity of plant samples, thus can extend the shelf-life of products by abating microorganism growth and undesirable reactions. Insignificant (0.01%) difference was found between lab-based oven dried and commercial spray dried samples on the proportion of *trans*-FT in *Cyperus esculentus* rhizomes (Vega-Morales et al. 2019), suggesting it is relatively stable under different drying conditions. Li et al. (2013) showed that freeze drying and sun drying improved the *trans*-FT content of *Allium macrostemon* Bunge extracts. Despite the higher cost, the authors advocated freeze drying as the most suitable drying method for *A. macrostemon* extracts, mainly due to very rapid sublimation of ice-water and preservation of metabolites at low temperature.

Microencapsulation is one of the food technologies employed to protect against polyphenol degradation and ensure its controlled delivery and release in the host (Fang and Bhandari 2010). The principle of liposomes is based on hydrophobic-hydrophilic interactions between lipid and water molecules to form a phospholipid bilayer surrounding the core component. Borrás-Linares et al. (2015) studied the permeability of free and liposome-encapsulated FT from *Hibiscus sabdariffa* on Caco-2 intestinal membrane model. Both FT forms were detected in apical-to-basolateral (Ap-Bas; into the cell) and basolateral-to-apical (Bas-Ap; out of the cell) directions of the transport medium. However, it seems that liposome encapsulation reduced the overall permeability of *H. sabdariffa* compounds, which may be due to the complex composition and possible interactions between compounds. Throughout individual 90 minutes assay period, FT concentration in the cells was higher than selected compounds quercetin, quercetin-3-glucoside and quercetin-3-glucuronide in Ap-Bas/Bas-Ap directions. This shows a more significant absorption of FT than other compounds in *H. sabdariffa* extract. In addition, the higher permeability in Bas-Ap direction indicates an efflux transport system of FT. Further encapsulation studies are still needed to improve the stability, absorption and bioconversion of FT and other HCAAT in intestinal model.

Other studies have detected HCAAT in processed products, though no comparison was made to unprocessed samples or different processing methods. Matsutomo, Stark, and Hofmann (2018) quantified *trans*-FT, *trans*-COT, *trans*-coumaroylphenetyramine, and *trans*-CIT in aged garlic (soaked in ethanol, then stored for 10 months at room temperature) at 98.1, 23.1, 0.2, 1.0 μg/g dry sample, respectively. In particular, *trans*-FT and *trans*-COT played important roles in antioxidant properties of the aged garlic extract, displaying stronger hydrogen peroxide scavenging and oxygen radical absorbance capacity than positive control ascorbic acid and parent compounds cinnamic, ferulic and *p*-coumaric acid. Moreover, *trans*-FT was isolated from rice fermented with fungus *Monascus pilosis* and exhibited 60% inhibition of DPPH compared to α-tocopherol (Cheng et al. 2010). Therefore, these findings suggest the potential application of HCAAT in processed functional foods.

Lipid oxidation is a free radical-catalyzed chain reaction that represents a major issue in the food industry. It results in the release of volatile compounds, off-flavours/odours of rancidity, deterioration of lipid's nutritional value and higher food waste. Synthetic antioxidants are effective to suppress radical chain reaction, but has raised safety concerns on human health (Lobo, Patil, Phatak, & Chandra, 2010). As a result, the use of natural antioxidants, such as HCAAT, to replace synthetic antioxidants, seems promising. Inhibition toward growth of several gram positive and negative bacteria by HCAAT further indicated its potential as food preservatives. In the U.S.A. and Japan, the use of cinnamic acid derivatives have been authorized and considered safe in food products (The Japan Food Chemical Research

Foundation 2014; U.S. Food and Drug Administration 2019). Thus, the application of HCAAT in the food industry can be accomplished by direct integration into food products or packaging material.

Parent compounds of HCAAT, such as ferulic and caffeic acid, have been included in dietary supplements to support neurocognitive health, skin anti-aging, bone and tissue protection (Neelam et al., 2019). Similarly, *p*-coumaric acid was studied as a component of topical cream to alleviate hyperpigmentation (Seo et al. 2011). Based on the above discussed potent biological activities in vivo and in vitro (also in Table 3), HCAAT could be incorporated in dietary supplements, drug medication or skin care products. Specifically, FT/CAT/COT has the potential for anti-inflammatory medication, FT/CAT for sunscreen or anti-cancer supplements, COT for AD treatment and glucose-lowering medication, and FT for neurocognitive support, though this requires more in vivo evidence before entering development process.

Conclusion and future studies

HCAAT are a group of plant secondary metabolites and play an important role in plant growth, development and defence. In addition to be naturally biosynthesised in plants, metabolic engineering and chemical synthesis have been employed to increase their production yield. These compounds have exhibited potential antioxidant, anti-inflammatory, anti-cancer, anti-diabetic and neuroprotective effects, as demonstrated by in vitro chemical assays, cell line studies and animal models. Due to these potential positive activities, HCAAT have application prospects in food and pharmaceutical industries. Several recommendations for future studies include: (*i*) Chemical synthesis of HCAAT at acceptable yields and low environmental impact. (*ii*) Further in vivo trials involving animal and human subjects. For instance, only one study has shown the anti-metabolic syndrome properties of FT. There's a strong likelihood that other HCAAT possesses a similar effect. (*iii*) Investigation on the bioactivities of *cis*-HCAAT. Although its presence could be an artifact of the isomerization procedure, *cis*-FT has shown equally potent anti-melanogenesis and neuroprotective effect as its *trans* counterparts. (*iv*) Additional in vitro assays on anti-bacterial and anti-parasitic activities of HCAAT. Past anti-bacterial studies of HCAAT have been conflicting. There is limited knowledge of HCAAT's anti-parasitic activity, aside from *Trypanosoma brucei*. (*v*) Other potential biological activities, such as effects on male reproduction (due to its NO-inhibition effect), regulation of the gut microbiota or anti-viral properties. (*vi*) Effect of food processing and technology on the chemistry, content, and bioactivity of HCAAT. Moreover, the detailed mechanism in intestinal absorption of free and encapsulated HCAAT remains to be elucidated. (*vii*) Direct HCAAT integration into food products and packaging. This may include its effect on the product's lipid oxidation levels, microbial counts, shelf life and consumer acceptance.

Disclosure statement

The authors declare no conflict of interest.

Abbreviations

AAA	aromatic amino acids
COT	coumaroyltyramine
CAT	caffeoyltyramine
CIT	cinammoyltyramine
COO	coumaroyloctopamine
COMT	caffeic-acid/5-hydroxyferulic acid O-methyltransferase
COX	cyclooxygenases
C4H	Cinnamate 4-hydroxylase
FO	feruloyloctopamine
FT	feruloyltyramine
HCAAT	tyramine-derived hydroxycinnamic acid amides
HSA	human serum albumin
LOX	lipooxygenases
LPS	lipopolysaccharides
PAL	phenylalanine ammonia-lyase
SIT	sinapoyltyramine
THT	hydroxycinnamoyl-CoA:tyramine N-(hydroxycinnamoyl)transferase
TYDC	tyrosine decarboxylase
TβH	tyramine β-hydroxylase
4CL	4-(hydroxy)cinnamoyl-CoA ligase.

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