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New Insights into Identification, Distribution, and Health Benefits of Polyamines and Their Derivatives

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ABSTRACT: Polyamines and their derivatives are ubiquitously present in free or conjugated forms in various foods from animal, plant, and microbial origins. The current knowledge of free polyamines in foods and their contents is readily available; furthermore, conjugated polyamines generate considerable recent research interest due to their potential health benefits. The structural diversity of conjugated polyamines results in challenging their qualitative and quantitative analysis in food. Herein, we review and summarize the knowledge published on polyamines and their derivatives in foods, including their identification, sources, quantities, and health benefits. Particularly, facing the inherent challenges of isomer identification in conjugated polyamines, this paper provides a comprehensive overview of conjugated polyamines' structural characteristics, including the cleavage patterns and characteristic ion fragments of MS/MS for isomer identification. Free polyamines are present in all types of food, while conjugated polyamines are limited to plant-derived foods. Spermidine is renowned for antiaging properties, acclaimed as antiaging vitamins. Conjugated polyamines highlight their anti-inflammatory properties and have emerged as the mainstream drugs for antiprostatitis. This paper will likely help us gain better insight into polyamines and their derivatives to further develop functional foods and personalized nutraceuticals.

KEYWORDS: *conjugated polyamines, spermidine, functional properties, nutraceuticals*

1. INTRODUCTION

Anton van Leeuwenhoek first discovered crystals in human semen in 1678, and they were later identified as spermine by A. Landenburg and J. Abel in 1888.[1] Spermine, therefore, is the most anciently recognized polyamine in the annals of human scientific inquiry. Polyamines (PAs) are a cluster of aliphatic and nitrogenous components with low molecular weight characterized by having two or more amino groups ($-NH_2$), such as diamine and putrescine, triamine and spermidine, and tetraamine, spermine, and agmatine.[2] They are ubiquitous across all life forms in microorganisms, plants, and animals.[3]

The human body sustains its polyamine levels through three sources: endogenous or de novo synthesis, intestinal microorganisms, and dietary intake from external sources.[4] Polyamines are present in various food sources, including animal, plant-derived, and microbial sources in free or conjugated forms.[2] Among free polyamines (FPAs), spermidine and spermine are the most common and abundant in foods, while putrescine and cadaverine are frequently found in fermented or spoiled food.[5] In plants, PAs are usually present in the conjugated form, and bond to hydroxycinnamic acids within plant organisms to form conjugated PAs (CPAs), also named phenolamides.[2,6] Thus, CPAs as plant-specialized metabolites are exclusively present in plant-derived foods. The CPA structure is characterized by the linkage of at least one hydroxycinnamic acid (for example, *p*-coumaric, ferulic, or/and caffeic acid) through an amide bond with a polyamine (putrescine, cadaverine, spermidine, or spermine)[6] (Figure 1). The combination of all the different hydroxycinnamic acid and polyamine building blocks, coupled with the possibility of partial N-acylations of polyamines, has led to the prediction of hundreds of CPAs predicted previously.[7,8] With new CPAs being continually discovered, the complete characterization of CPAs in food remains an ongoing research frontier due to their complexity and functions.

PAs confer various health benefits. As the most widely recognized FPA, spermidine is hailed as the "antiaging vitamin" by activating cellular autophagy.[9,10] According to Swedish Nutrition Recommendations, the daily amount of spermidine is recommended as approximately 30 mg for males and 25 mg for females.[10,11] With the continuous finding of CPAs in food, there has been a growing recognition and reporting of their functional properties, especially antiprostatitis[12] and antityrosinase.[13] Based on the numerous benefits of polyamines for human health, Europe has initiated clinical trials on some polyamines, and the global market for polyamines is expected to expand significantly if scientific evidence is sufficiently provided. Noteworthily, there are significant variations in the

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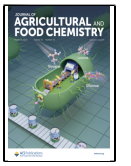

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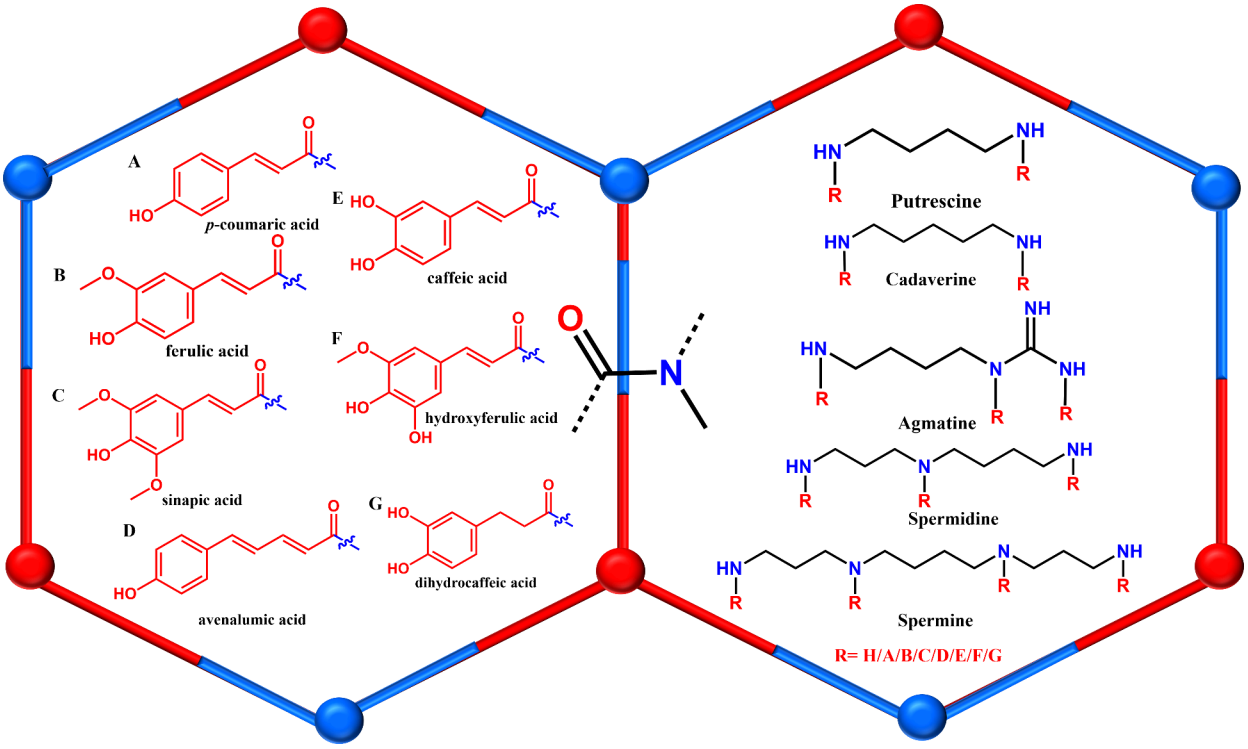

Figure 1. Structural origin and characteristics of conjugated polyamines.

Table 1. Ranges of Average Free Polyamine Contents in Food (mg/kg)

Food Products	Putrescine	Spermidine	Spermine	Agmatine	References
Plant-derived					
Vegetable					
Aubergine, beet, broccoli, cabbage, cauliflower, carrot, celeriac, celery, courgette, cucumber, eggplant, green beans, green pepper, garlic, ginger, lettuce, mushroom, maize, okra, onion, potato, pumpkin, parsley, spinach, sauerkraut, tomato	0.5−146.0	nd-88.6	nd-18.4	2.2−6.7	26,27,29,33−35
Fruits					
Apple, avocado, banana, cherry, dates, figs, grapes, kiwi, lime, mandarin, mango, melon, orange, papaya, pear, peach, pineapple, prune, strawberry, watermelon	nd-137.1	nd-14.2	nd-5.1	-	24,30,34,37
Cereals					
Corn, rice, millet, wheat germ, oat bread, bread, pasta, white bread, flour, whole grain	0.2−62.1	0.41−354.1	nd-146.1	nd-4.7	24,25,27,37
Legumes					
Chickpeas, green peas, lentils, peas, white beans, red kidney beans, soybean, soybean sprouts, soybean milk, tofu, soy sauce, miso	nd-88.1	nd-207.1	nd-69.1	nd-30.0	23,25,27,28
Roasted nuts					
Almonds, cashew, chestnuts, hazelnut, peanut, pistachios, seeds	0.8−43.0	4.6−55.6	6.5−33.4		24,25,32
Beverages					
Apple juice, beer, coffee, grapefruit juice, orange juice, pineapple juice, red wine, tea, white wine	nd-98.6	nd-38.1	nd-59.0	nd-42.0	25,27
Animal-derived					
Meat					
Beef, beef liver, chicken, chops, cooked meat, duck, lamb, meat, pork, rabbit, sirloin, turkey, veal	0.1−10.1	0.1−19.0	0.1−197	nd-27.0	25,27,39,45
Meat products					
Bacon, fermented meat, pork ham, mortadella, sausage, salami, Spanish sausage, spicy sausage	nd-14.2	nd-6.1	nd-35.7	nd-43.0	27,38
Milk and milk products					
Cheese, full cream, milk, breast milk, Semiskimmed, Soya milk, yogurt	nd-653.0	nd-199.5	nd-3.4	nd-19.0	2,15,27,40,41
Fish and seafood products					
Calamari, cod, crab, fish sauces, hake, mackerel, oysters, salmon, sardine, scallops, shrimp, tuna, white fish	0−122.0	0−37.0	0−26.0	nd-401.0	25,27,35
Egg	3.1−10	1−4.0	nd-1.0	-	2

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types and levels of polyamines in different foods, leading to different health benefits.[6]

In recent years, with the ongoing advancement of research on polyamines in food, there has been a continuous update of reviews on the types, quantities, and potential benefits of polyamines in food.[5,7,11,14−17] However, previous reviews' attention toward polyamines in food has been predominantly centered on the free form, while less attention is paid to the conjugated form with a wider variety of types, quantities, and potential benefits. To the best of our knowledge, extant literature solely encompasses the review by Wang et al. elucidating the chemical structures and functionalities of CPAs within food matrices.[6] Nonetheless, in light of recent advancements in the identification of distinctive CPAs within bee pollen and other plant foods, it is necessary to summarize the distribution and content of polyamines with free and conjugated forms in foods for a renewed understanding of polyamines. This paper aims to comprehensively review the latest research on the identified polyamines with the free and conjugated forms, their levels in various foods, and the potential health benefits, thereby providing valuable insights for the development of functional foods and personalized nutraceuticals.

2. IDENTIFICATION, SOURCES, AND QUANTITIES OF FPAS

2.1. Identification. Free polyamines in foods are mainly putrescine, spermidine, spermine, and agmatine.[18] The identification methods for polyamine determination in food primarily rely on chromatographic separation, such as gas chromatography, thin-layer chromatography, and high-performance liquid chromatography, and various detection techniques coupled with chromatography, including UV, fluorescence, and mass spectrometry.[19,20] Due to polyamine' low UV absorption and fluorescence yields, complex derivatization is often used for UV or fluorescent detection. LC-MS/MS has emerged as a specific and sensitive alternative without needing derivatization.[21] Electrochemical sensors/biosensors offer a cost-effective, time-efficient option for rapid polyamine detection in foods, exhibiting low detection limits and high selectivity for routine screenings.[22] In addition, commercially available standards for the common FPAs make the identification in the complex foods easier and more accurate.

2.2. Sources and Quantities. The variability of polyamine contents in food is attributed to their origin, growing conditions, harvesting, storage, and processing.[23−29] As seen in Table 1, vegetables and fruits have higher levels of putrescine, with the content in sauerkraut reaching as high as 146 mg/kg.[15,30−34] Additionally, oranges, mandarins, and mangoes exhibit high putrescine contents, 117.6, 122, and 80 mg/kg,[32] respectively (Table 1). In beverage products, grapefruit and orange juice also contain elevated levels of putrescine.[25,27] The high levels of putrescine in some vegetables, such as sauerkraut, spinach, and peas, is attributed to the presence of spoilage bacteria to produce putrescine from ornithine by amino acid-decarboxylase, mainly *Enterobacteriaceae* and *Clostridium spp.*.[35,36] Additionally, mushrooms and pumpkins also contain abundant spermidine and spermine. Nuts present the higher spermidine and spermine contents than fresh vegetables and fruits. Cereals and legumes present the highest contents of spermidine and spermine. Wheat germ and soybeans stand out particularly with the respective values of 354.1 and 207.1 mg/kg of spermidine and 146.1 and 69.1 mg/kg of spermine (Table 1).[32,37] Therefore, currently available spermidine supplement products on the market are mainly extracted from wheat germ.

In animal-derived foods, the content of polyamines is also closely related to their source, processing, and storage conditions.[2] Meat and its products contain high concentrations of spermidine and spermine, especially spermine.[15,38−41] In fresh meat (including beef, chicken, duck, lamb, pork, and rabbit), the content of spermine exceeds 20 mg/kg, while the highest levels are found in the liver, for example, 197 mg/kg in beef liver and 137 mg/kg in chicken liver (Table 1).[42−44] There is no significant difference in the contents of spermidine and spermine between meat and meat products.[45] Fresh cow's milk and eggs have low polyamine content, while fermented dairy products present higher levels of putrescine and spermidine.[2,31,32] Particularly in cheese (cheddar, matured), putrescine content can reach up to 653 mg/kg, and the agmatine content can reach 199 mg/kg.[5] As a fermented food, cheese undergoes microbial fermentation, producing high levels of putrescine. In fish and seafood, the contents of spermine and spermidine are generally lower than those in meat products, but higher than those in fresh milk and eggs.

Several culinary practices have been reported to change the profiles of FPAs in food, although experimental data are still scarce.[35,46] A study involving vegetables and meats observed that different domestic cooking processes significantly influenced polyamine levels in food. Boiling and grilling reduced 64% of polyamine levels, while remaining practically unmodified by microwave and sous vide cooking.[35] In another investigation, it was discerned that roasting, grilling, and frying precipitated a notable decline of 40−60% in spermidine and spermine levels within fresh chicken breast, whereas boiling and stewing reduced 5% to 25%.[46] Future research should focus on the impacts of culinary processing on polyamine contents in foods, for assessing the actual levels of polyamine intake by humans from foods.

3. IDENTIFICATION, SOURCES, AND QUANTITIES OF CPAS

3.1. Identification. The richness of synthetic precursors leads to the structural diversity of CPAs, over thousands in theory. CPAs can be further classified into four subcategories, based on the number of substituent groups on the amine structure, including monosubstituted, bisubstituted, trisubstituted, and tetrasubstituted amides.[8,47] High-performance liquid chromatography-high-resolution mass spectrometry (HPLC-HRMS) is widely utilized to identify numerous CPAs.[13,48] Nevertheless, prevailing methodologies primarily analyze a restricted subset of recognized CPAs within a specific plant specimen, facing three additional challenges: (1) The presence of *cis*−*trans* isomers in hydroxycinnamic acids. For example, di-*p*-coumaroyl spermidine has been detected with four *cis*−*trans* isomers in previous research: N^1-(Z), N^{10}-(Z)-; N^1-(Z), N^{10}-(E)-; N^1-(E), N^{10}-(Z)-; and N^1-(E), N^{10}-(E)-di-*p*-coumaroyl spermidine.[11] (2) Multiple positional isomers. Polyamines have at least two free amine groups as the variable linkage positions with hydroxycinnamic acids. For example, the monosubstituted spermidine exhibits at least three isomers, like N^1-, N^5-, or N^{10}-*p*-coumaroyl spermidine. (3) Some polyamine substituents, such as hexoside and caffeoyl residues, can easily be confused. Multiple isomers of CPAs have been reported in recent years, but accurate structural character-

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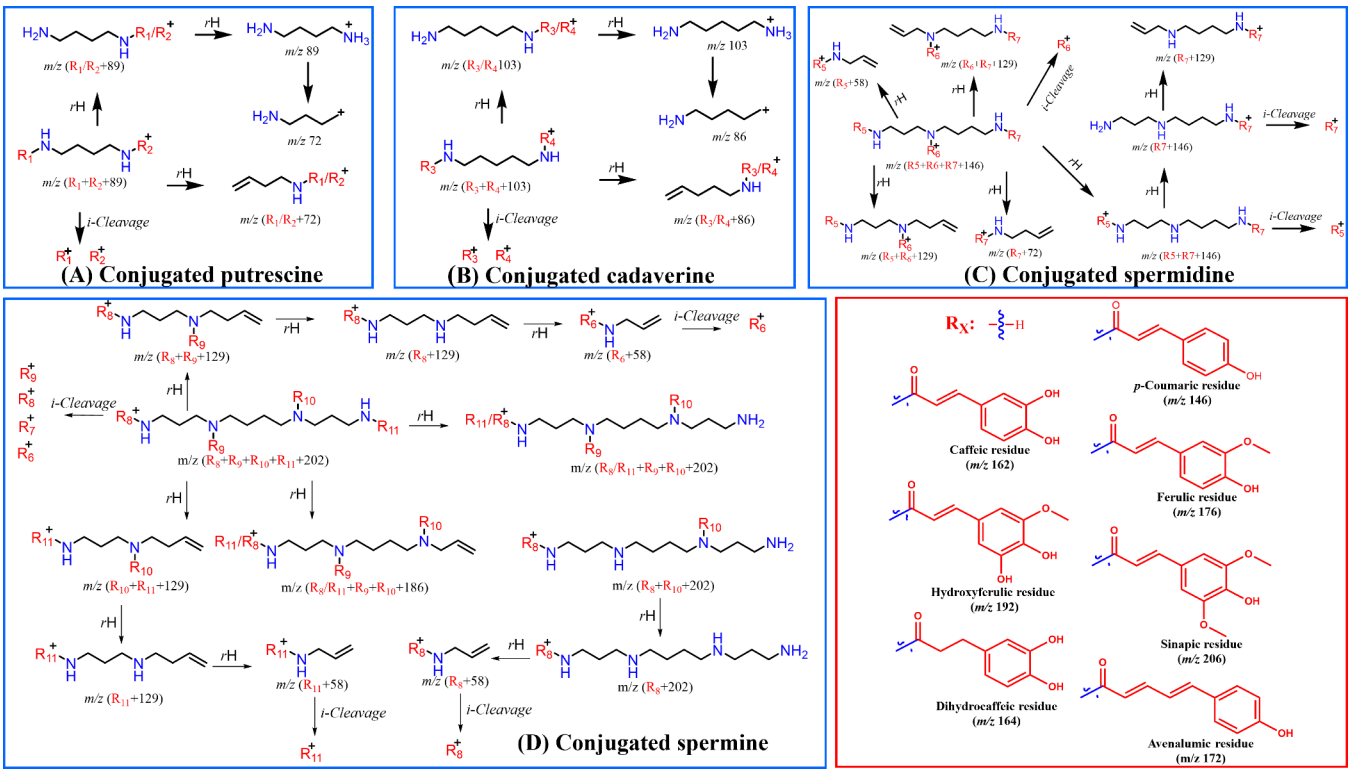

Figure 2. Fragment cleavage patterns of mass spectra (ESI) of conjugated polyamines.

ization of these isomers has not yet been achieved. Furthermore, numerous studies indicate that isomers often exhibit significant differences in functional activities.[49,50] Based on the HPLC-HRMS technique, this review provides a comprehensive summary of CPAs' structural features, including the cleavage patterns and characteristic ion fragments (Figure 2 and Table 2) for isomer identification.

3.1.1. Characteristic Ions of Hydroxycinnamic Residues. The MS/MS+ spectra of CPAs usually present some particular fragment ions (Figure 2 and Table 2). Quasi-molecular ions usually consecutively lose one or more, 146 amu (*p*-coumaroyl residue), 162 amu (caffeoyl residue), 164 amu (dihydro caffeoyl residue), 172 amu (avenalumoyl residue), 176 amu (feruloyl residue), 192 amu (hydroxy feruloyl residue), or/and 206 amu (sinapoyl residue), through *H* rearrangement.[11,16] Meanwhile, quasi-molecular ions undergo *i*-cleavage to generate fragment ions *m*/*z* 147, *m*/*z* 163, *m*/*z* 165, *m*/*z* 173, *m*/*z* 177, *m*/*z* 192, or/and *m*/*z* 207 in the MS/MS+ spectra, respectively responding *p*-coumaroyl, caffeoyl, dihydro caffeoyl, avenalumoyl, feruloyl, hydroxy feruloyl, or/and sinapoyl residue.

3.1.2. cis−trans Isomers. Hydroxycinnamic acids usually present *cis*−*trans* isomers, thus resulting in multiple isomers of CPAs, such as tri-*p*-coumaroyl spermidine isomers in Lycium berry and bee pollen.[17,51] Generally, HRMS is unable to differentiate between *cis* and *trans* isomers. In recent years, Seon Beom Kim and his colleagues[52] have identified some *cis*−*trans* isomers of CPAs through nuclear magnetic resonance (NMR) spectroscopy. In recent investigations, integrating compound polarity and maximum UV absorption wavelength can identify distinct isomeric CPA forms.[51] The *cis*-isomer of hydroxycinnamic acids displays a lower maximal UV absorption wavelength than its *trans*-isomeric counterpart. The formation of a $\pi-\pi$ conjugate bond in the *trans*-isomer, facilitated by steric hindrance, leads to a red shift in the UV absorbance spectrum.[53] Furthermore, *cis*-isomers typically exhibit higher dipole moments than *trans*-isomers, resulting in a slightly stronger manifestation of polarity (hydrophilicity) in *cis*-isomers than *trans*-isomers.[53] For instance, in rapeseed bee pollen,[13] N^1-(Z), N^{10}-(Z)-; N^1-(Z), N^{10}-(E)-; N^1-(E), N^{10}-(Z)-; and N^1-(E), N^{10}-(E)-di-*p*-coumaroyl spermidine displayed the red shift of UV maximum absorption wavelength, respectively, 274, 282, 292, and 306 nm, and the decrease of polarity.[11] Each additional *trans*-*p*-coumaroyl results in a red shift, plus 8−14 nm in the UV maximum absorption wavelength of *cis*-*p*-coumaroyl. Consequently, it becomes feasible to ascertain the *cis*−*trans* isomers of CPAs by amalgamating UV maximum absorption wavelength and chromatographic behavior using HPLC-DAD-HRMS.

3.1.3. Positional Isomer. Some specific fragment ions in MS/MS spectra corroborate the amidated position of hydroxycinnamic acids with polyamines. These fragment ions aid in identifying the free N position within CPAs featuring unsaturated substitutions, such as disubstituted spermidine and trisubstituted spermine. In Figure 2C,D, typical fragment ions *m*/*z* (R_X + 58) and *m*/*z* (R_X + 72) can ascertain hydroxycinnamic acids conjugated at positions N1 and N10, respectively. Take di-*p*-coumaroyl feruloyl spermidine as an example (refs 11 and 16 and Figure 2B), the fragment ions *m*/*z* 204 (146 + 58), resulted from the cleavage of C4 and N5 by *H* rearrangement, indicating one *p*-coumaroyl residue substituted at N1. The *m*/*z* 218 (146 + 72) indicates another *p*-coumaroyl residue substituted at N10. Moreover, the fragment ion *m*/*z* (R8 + R9 + 129) (Figure 2) indicates R8 and R9 substituted at two adjacent N positions. For instance, N^1-hydroxyferuloyl-N^5-*p*-coumaroyl-N^{14}-feruloyl spermine,[11] the fragment ions *m*/*z* 250 (192 + 58) and *m*/*z* 234 (176 + 58) indicate one hydroxy feruloyl and feruloyl residues substituted

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Table 2. Sources and MS Characteristics of Conjugated Polyamines in Foods

CPAs	Sources	$(M + H)^+$ (m/z)	Fragments (m/z)	References
p-Coumaroyl putrescine	Rye products, rice, tea flowers (*Camellia sinensis*), sunflower bee pollen	235	119, 147	16,73,74
Caffeoyl putrescine	Rye products, rice, pepper (*capsicum spp.*)	251	135, 163	62,72,74
Feruloyl putrescine	Barley, beer, rye products, rice, pollen, pepper (*capsicum spp.*)	265	145, 177	62,71,74
Dimethoxy cinnamoyl putrescine	Rye products	279	89, 191	74
Hydroxyferuloyl putrescine	Rye products	281	89, 193	74
Sinapoyl putrescine	Rice, Lycium berry	295	89, 119, 207	58,72
Di-*p*-coumaroyl putrescine	Bee pollen (apricot, broad bean, sunflower, pear, hawthorn, kiwifruit)	381	89, 119, 147, 218, 235	11,17,73
p-Coumaroyl caffeoyl putrescine	Broad bean bee pollen, tea flowers	397	89, 147, 163, 218, 235, 251	11,16
p-Coumaroyl feruloyl putrescine	Broad bean bee pollen, tea flowers, maize bread, corn bran	411	89, 147, 177, 218, 235, 265	11,16,63
Dicaffeoyl putrescine	Broad bean bee pollen, lycium berry	413	89, 145, 163, 234, 251	11,64
Feruloyl caffeoyl putrescine	Broad bean bee pollen	427	234, 251, 265	11
Diferuloyl putrescine	Fabaceae bee pollen, corn bran	441	89, 265	68
p-Coumaroyl cadaverine	Wheat	249	103, 147	59
Diferuloyl cadaverine	Maize	455	103, 177	76
p-Coumaroyl spermidine	Rye products	292	91, 119, 147, 204	74
Caffeoyl spermidine	Rye products, rice, tea flowers	308	146, 163, 220	16,74
Feruloyl spermidine	Rye products, rice, barley, beer, Tea flowers	322	146, 177, 234	16,71
Di-*p*-coumaroyl spermidine	Bee pollen (rapeseed, phellodendron, tea, buckwheat), rye products, rice	438	72, 119, 147, 204, 292	11,74,130
p-Coumaroyl caffeoyl spermidine	Rye products, rice	454	147, 163, 292, 308	74,130
p-Coumaroyl feruloyl spermidine	Tea flowers, brewer's spent grain extracts	468	147, 177, 204, 117, 322	16,57
Dicaffeoyl spermidine	Tea flowers, rye products, barley, beer,	470	163, 308	16,71,74
Di(dihydrocaffeoyl) spermidine	Potato	474	165, 222, 293, 310	60
Caffeoyl feruloyl spermidine	Tea flowers, barley, beer,	484	163, 177, 308, 322	16,71
Diferuloyl spermidine	Tea flowers, rye products	498	177, 322	16,74
Disinapoyl spermidine	Rice	558	207, 352	72
Tri-*p*-coumaroyl spermidine	Tea flowers, saffron, bee pollen (sunflower, plums, pear, oil-tea, tea, phellodendron, apricot, hawthorn, kiwi fruit, broad bean, melon, buckwheat, rose broad bean)	584	147, 204, 275, 292, 420, 438	30,66
Di-*p*-coumaroyl caffeoyl spermidine	Bee pollen (apricot, rose, oil-tea, broad bean, tea, phellodendron)	600	147, 163, 204, 218, 275, 292, 318, 420, 438, 454706	11
Di-*p*-coumaroyl feruloyl spermidine	Bee pollen (oil-tea and tea)	614	147, 177, 204, 248, 275, 292, 322, 348, 438, 450, 468	11
Dicaffeoyl *p*-coumaroyl spermidine	Bee pollen (broad bean, oil-tea, tea, phellodendron, buckwheat)	616	147, 163, 204, 220, 436, 454, 470	11,17
p-Coumaroyl feruloyl spermidine hexoside	Foxtail millet	630	147, 177, 308, 338, 454, 484	54
Di-*p*-coumaroyl hydroxyferuloyl spermidine	Bee pollen (apricot, tea, phellodendron, buckwhea)	630	147, 193, 204, 264, 275, 292, 338, 438, 466, 484	11
Lycibarbarspermidines N	Lycium berry	632	163, 220, 291, 308	61,67
Tricaffeoyl spermidine	Bee pollen (apricot, tea, phellodendron, buckwhea)	632	163, 220, 291, 308, 452, 470	11
Lycibarbarspermidines A	Lycium berry	634	163, 206, 309, 310, 382, 472	61,67
Lycibarbarspermidines B	Lycium berry	634	165, 222, 308, 311, 470, 472	61,67
Lycibarbarspermidines C	Lycium berry	634	163, 206, 309, 310, 382, 472	61,67
Lycibarbarspermidines D	Lycium berry	634	165, 222, 308, 311, 470, 472	61,67
Lycibarbarspermidines H	Lycium berry	636	163, 220, 311, 474, 531	61,67

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Table 2. continued

CPAs	Sources	$(M + H)^+$ (m/z)	Fragments (m/z)	References
Lycibarbarspermidines I	Lycium berry	636	165, 208, 313, 472, 474	61,67
Lycibarbarspermidines J	Lycium berry	636	163, 220, 311, 474, 531	61,67
Tris(dihydrocaffeoyl) spermidine	Potato	638	165, 222, 293, 457, 474	60
Triferuloyl spermidine	Rhus chinensis bee pollen	674	145, 177, 234, 305, 348, 480, 498	61,67
Diferuloyl-hydroxyferuloyl spermidine	Rhus chinensis bee pollen	690	145, 177, 234, 305, 496, 514	11
Diferuloyl sinapoyl spermidine	Rice	705	177, 207, 234, 353, 499, 529	72
Dihydroxyferuloyl-feruloyl spermidine	Rhus chinensis bee pollen	706	145, 177, 193, 250, 264, 321, 338, 364, 497, 512, 530	11
Lycibarbarspermidines O	Lycium berry	794	-	61,67
Lycibarbarspermidines E	Lycium berry	796	162, 164, 309, 310, 381, 472, 634	61,67
Lycibarbarspermidines F	Lycium berry	796	162, 164, 309, 310, 381, 472, 634	61,67
Lycibarbarspermidines G	Lycium berry	796	368, 383, 472, 634	61,67
Lycibarbarspermidines M	Lycium berry	798	311, 369, 383, 474, 636	61,67
Lycibarbarspermidines K	Lycium berry	798	221, 369, 383, 473, 474, 636	61,67
Lycibarbarspermidines L	Lycium berry	798	221, 369, 383, 473, 474, 636	61,67
Diferuloyl spermidine-dihexoside	Foxtail millet	821	177, 307, 483, 659	54
Kukoamines A/B	Lycium berry, potatoes and tomatoes	531	165, 222, 367	78
Di-*p*-coumaroyl-diacetyl spermine	Corn poppy bee pollen	579	147, 171, 204, 275, 287, 313, 391, 416	11
Tri-*p*-coumaroyl spermine	Chrysanthemum bee pollen	641	147, 204, 275, 349, 421, 495686	11
Di-*p*-coumaroyl-caffeoyl spermine	Rapeseed bee pollen	657	147, 163, 204, 220, 275, 349, 437, 495, 511	11
Feruloyl-di-*p*-coumaroyl spermine	Rapeseed bee pollen	671	147, 177, 204, 234, 275, 305, 349, 451, 495, 525	11
Di-*p*-coumaroyl hydroxy avenalumoyl spermine	Corn poppy bee pollen	683	147, 204, 275, 317, 374, 391, 417, 519, 537	11
Di-*p*-coumaroyl hydroxy feruloyl spermine	Bee pollen (rapeseed and buckwheat)	687	147, 204, 250, 275, 321, 349, 395, 495, 541	11
Tris(dihydrocaffeoyl) spermine	potato	695	165, 222, 293, 367, 457, 531	60
Hydroxyferuloyl-*p*-coumaroyl caffeoyl spermine	Rapeseed bee pollen	703	147, 193, 220, 250, 275, 291, 321, 349, 395, 467, 511, 541, 557	11
Hydroxyferuloyl-*p*-coumaroyl-feruloyl spermine	Bee pollen (rapeseed and buckwheat)	717	147, 177, 193, 234, 250, 275, 305, 321, 349, 395, 421, 467, 525	11
Tetra-*p*-coumaroyl spermine	Greek chamomile, bee pollen (chrysanthemum, tea, sunflower, buckwheat, brazilian)	787	147, 204, 275, 421, 495, 623, 641	11,65
Tri-*p*-coumaroyl-hydroxy feruloyl spermine	Rapeseed bee pollen	833	147, 204, 250, 275, 291, 321, 495, 541, 641, 669, 687	11
Caffeoyl-di-*p*-coumaroyl-hydroxy feruloyl spermine	Rapeseed bee pollen	849	147, 163, 220, 250, 275, 291, 321, 437, 467, 494, 511, 557, 657, 685, 703	11
Tetracaffeoyl spermine	Rapeseed bee pollen	851	163, 220, 291, 365, 453, 527, 689	11
Tetra(dihydrocaffeoyl) spermine	Potato	859	165, 222, 293, 457, 694	60
Tricaffeoyl-feruloyl spermine	Rapeseed bee pollen	865	147, 163, 193, 220, 250, 321, 467, 527, 557, 689, 703, 719	11
Tricaffeoyl-hydroxy feruloyl spermine	Bee pollen (rapeseed and buckwheat)	881	163, 193, 220, 250, 291, 321, 453, 483, 527, 557, 701, 719	11
Feruloyl-dicaffeoyl-hydroxy feruloyl spermine	Rapeseed bee pollen	895	163, 177, 193, 220, 250, 291, 321, 467, 510, 539, 57, 571, 701, 719, 733	11

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Table 2. continued

CPAs	Sources	$(M + H)^+$ (m/z)	Fragments (m/z)	References
Dihydroxy feruloyl-dicaffeoyl spermine	Rapeseed bee pollen	911	163, 193, 220, 250, 291, 321, 483, 557, 587, 719, 748	11
p-Coumaroyl agmatine	Tea flowers, barley, beer, rye products	277	131, 147	16,71,74
Caffeoyl agmatine	Tea flowers, barley, beer, rye products	293	131, 163	16,71,74
Feruloyl agmatine	Tea flowers, barley, beer, rye products	307	131, 177	16,71,74
Feruloyl methylagmatine	rye products	321	177,	74
Sinapoyl agmatine	Barley, rye products	337	131, 207	71,74
p-Coumaroyl agmatine hexoside	Barley	439	131, 277	71
Feruloyl agmatine hexoside	Barley	469	131, 177, 334	71
Sinapoyl agmatine hexoside	Barley	499	131, 207, 337	71

at N1 or N14, respectively. The fragment ion m/z 467 (192 + 146 + 129) indicates hydroxy feruloyl and *p*-coumaroyl residue substituted at two adjacent N positions. Thus, this compound can be confirmed as N^1-hydroxyferuloyl-N^5-*p*-coumaroyl-N^{14}-feruloyl spermine.

3.1.4. Substituting Isomers. In recent years, many studies have reported the presence of *O*-hexoside derivatives in CPAs.[54,55] Their characteristics are the simultaneous conjugation of hydroxycinnamic or/and *O*-hexoside residue with polyamines, such as diferuloyl spermidine-dihexoside and Lycibarbarspermidines A, B, C, D, and E (Table 2).[54,55] In the MS/MS+ spectra of CPA, *O*-hexoside residue presents specific fragment ions, losing 162 amu (hexoside). As mentioned in section 3.1.1, caffeoyl residue also shows the same loss of 162 amu. This will confuse determining whether hexoside or caffeoyl residue when losing 162 amu in the MS/MS spectra of CPAs. The same situation also occurs in 146 amu (*p*-coumaroyl or pentoside residue). In MS/MS spectra, the hydroxycinnamic acid residue undergoes *i*-cleavage, and protonation occurs in the hydroxycinnamic acid residue. On the other hand, hexoside residue usually undergoes a neutral loss.[8] Therefore, there are clear hydroxycinnamic residues in the MS/MS+ spectrum, such as the presence of the m/z 163 fragment ion for the caffeoyl residue, but the absence of m/z 163 fragment ion (hexoside residue) in the MS/MS+ spectrum. Therefore, by observing the presence of protonated fragment ions or a neutral loss, it can be easily determined which residue of glycosides or hydroxycinnamic residue is conjugated in CPAs.

3.2. Sources and Quantities. CPAs naturally occur in plant-derived foods from the condensation reaction between CoA esters of hydroxycinnamic acids and aliphatic/di/poly amine groups.[56] CPAs have been reported to be widely present in the *Poaceae* and *Solanaceae* families, such as barley, wheat, rice, maize, potato, tomato, Lycium berry, bee pollen, and their related food products (Table 2).[57−68] So far, about 80 different types of CPAs have been identified in edible plants (Table 2), including 12 conjugated putrescine, 2 conjugated cadaverine, 39 conjugated spermidine, 20 conjugated spermine, and 8 conjugated agmatine. Notably, bee pollen is evidenced to possess abundant CPAs;[11,13,69,70] for example, the 31 CPAs and their 33 *cis*−*trans* isomers were observed in 20 types of monofloral bee pollen, constituting nearly half of the total identified CPAs in foods.[11] The 31 CPAs include 5 conjugated putrescines, 10 conjugated spermidines, and 16 conjugated spermines. Among the analyzed bee pollen samples, it is noteworthy that rapeseed bee pollen exhibits the most diversity of CPAs, a total of 13 distinct types, followed by buckwheat with 9 CPAs; both broad bean and tea bee pollen contain 8 CPAs. Nine conjugated spermines (di-*p*-coumaroyl-caffeoyl spermine, feruloyl-di-*p*-coumaroyl spermine, hydroxy feruloyl-*p*-coumaroyl caffeoyl spermine, tri-*p*-coumaroyl-hydroxy feruloyl spermine, caffeoyl-di-*p*-coumaroyl-hydroxy feruloyl spermine, tetracaffeoyl spermine, tricaffeoyl-feruloyl spermine, feruloyl-dicaffeoyl-hydroxy feruloyl spermine, and dihydroxy feruloyl-dicaffeoyl spermine) are exclusively found to exist in rapeseed bee pollen.[11]

Furthermore, many CPAs have been discovered in cereals such as rye, barley, rice, maize, and their related products (Table 2).[71−74] For example, coumaroyl caffeoyl spermidine, coumaroyl feruloyl spermidine, caffeoyl feruloyl spermidine, dicaffeoyl spermidine, dicoumaroyl spermidine, and coumaroyl dimethoxycinnamate spermine have been found in fermented

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Table 3. Contents of Conjugated Polyamines in Foods

CPAs	Contents (mg/g)	Sources	Reference standards	References
p-Coumaroyl putrescine	0.005−0.015	Rice	*p*-Coumaric acid	72
Feruloyl putrescine	0−0.0005	Rice	*p*-Coumaric acid	72
Tri-*p*-coumaroyl spermine	1.28	Bee pollen	Tetra-*p*-coumaroyl spermine	11
Tetra-*p*-coumaroyl spermine	0.11−7.35	Bee pollen	Tetra-*p*-coumaroyl spermine	11
N^1,N^{10}-Di-*p*-coumaroyl-N^{14}-hydroxyferuloyl spermine	0.83−1.64	Bee pollen	Tetra-*p*-coumaroyl spermine	11
N^1,N^{10}-Di-*p*-coumaroyl-N^{14}-caffeoyl spermine	0.41	Bee pollen	Tetra-*p*-coumaroyl spermine	11
N^1-Hydroxyferuloyl-N^5-*p*-coumaroyl-N^{14}-caffeoyl spermine	1.11	Bee pollen	Tetra-*p*-coumaroyl spermine	11
N^1-Hydroxyferuloyl-N^5-*p*-coumaroyl-N^{14}-feruloyl spermine	0.36−1.11	Bee pollen	Tetra-*p*-coumaroyl spermine	11
N^1-Feruloyl-N^5, N^{14}-di-*p*-coumaroyl spermine	0.22	Bee pollen	Tetra-*p*-coumaroyl spermine	11
N^1,N^{14}-Di-*p*-coumaroyl-N^5-hydroxyavenalumoyl spermine	3.17	Bee pollen	Tetra-*p*-coumaroyl spermine	11
N^1-Caffeoyl-N^5, N^{10}-di-*p*-coumaroyl-N^{14}-hydroxyferuloyl spermine	0.25	Bee pollen	Tetra-*p*-coumaroyl spermine	11
N^1,N^5,N^{10}-tri-*p*-coumaroyl-N^{14}-hydroxyferuloyl spermine	0.69	Bee pollen	Tetra-*p*-coumaroyl spermine	11
Di-*p*-coumaroyl putrescine	0.69−2.98	Bee pollen	Di-*p*-coumaroyl putrescine	11
Dicaffeoyl putrescine	1.40	Bee pollen	Di-*p*-coumaroyl putrescine	11
Feruloyl caffeoyl putrescine	0.90	Bee pollen	Di-*p*-coumaroyl putrescine	11
p-Coumaroyl feruloyl putrescine	1.35	Bee pollen	Di-*p*-coumaroyl putrescine	11
N^1,N^{10}-Di-*p*-coumaroyl-N^5-caffeoyl spermidine	0.38−26.17	Bee pollen	Tri-*p*-coumaroyl spermidine	11
Tri-*p*-coumaroyl spermidine	0.85−26.89	Bee pollen	Tri-*p*-coumaroyl spermidine	11
N^1-*p*-Coumaroyl-N^5,N^{10}-dicaffeoyl spermidine	0.36−1.86	Bee pollen	Tri-*p*-coumaroyl spermidine	11
Triferuloyl-spermidine	1.16	Bee pollen	Tri-*p*-coumaroyl spermidine	11
N^1,N^5-Di-*p*-coumaroyl-N^{10}-hydroxyferuloyl spermidine	0.75	Bee pollen	Tri-*p*-coumaroyl spermidine	11
N^1,N^{10}-Dihydroxyferuloyl-N^5-feruloyl spermidine	13.2	Bee pollen	N^1(E),N^{10}(E)-Dihydroxyferuloyl-N^5(E)-feruloyl spermidine	11
N^1,N^{10}-diferuloyl-N^5-hydroxyferuloyl spermidine	0.56	Bee pollen	N^1(E),N^{10}(E)-Dihydroxyferuloyl-N^5(E)-feruloyl spermidine	11
Tetracaffeoyl spermine	0.74	Bee pollen	Tetracaffeoyl spermine	11
N^1,N^5,N^{10}-Tricaffeoyl-N^{14}-hydroxy feruloyl spermine	1.06	Bee pollen	Tetracaffeoyl spermine	11
N^1,N^{14}-Dihydroxyferuloyl-N^5,N^{10}-dicaffeoyl spermine	0.11	Bee pollen	Tetracaffeoyl spermine	11
N^1,N^5,N^{10}-Tri-caffeoyl-N^{14}-feruloyl spermine	0.38	Bee pollen	Tetracaffeoyl spermine	11
N^1-Feruloyl-N^5, N^{10}-dicaffeoyl-N^{14}-hydroxyferuloyl spermine	0.21	Bee pollen	Tetracaffeoyl spermine	11
Di-*p*-coumaroyl spermidine	0.29−8.33	Bee pollen	Di-*p*-coumaroyl spermidine	11
p-Coumaroyl caffeoyl putrescin	1.4	Bee pollen	*p*-Coumaroyl caffeoyl putrescin	11
N^1,N^{14}-di-*p*-coumaroyl-N^5,N^{10}-diacetyl spermine	5.53	Bee pollen	N^1,N^{14}-Di-*p*-coumaroyl-N^5,N^{10}-diacetyl spermine	11
Tricaffeoyl spermidine	0.27−3.27	Bee pollen	Tricaffeoyl spermidine	11
N^1,N^5-Di-*p*-coumaroyl-N^{10}-feruloyl spermidine	0.23−0.26	Bee pollen	N^1,N^5-Di-*p*-Coumaroyl-N^{10}-feruloyl spermidine	11
Caffeoyl putrescine	0.022−0.28	Potato tubers	Dihydrocaffeic acid	60
N^1,N^{14}-di(dihydrocaffeoyl) spermine	0.022−0.28	Potato tubers	Dihydrocaffeic acid	60
N^1,N^{10}-di(dihydrocaffeoyl) spermidine	0.022−0.28	Potato tubers	Dihydrocaffeic acid	60
N^1,N^5,N^{14}-Tris(dihydrocaffeoyl) spermin	0.022−0.28	Potato tubers	Dihydrocaffeic acid	60
N^1,N^5,N^{10}-Tris(dihydrocaffeoyl) spermidine	0.022−0.28	Potato tubers	Dihydrocaffeic acid	60
N^1,N^5,N^{10}-Tris(dihydrocaffeoyl) spermidine	0.022−0.28	Potato tubers	Dihydrocaffeic acid	60
Caffeoyl putrescine	72.9	Purple potato extract	Spermine	79
Caffeoyl spermine	2.8	Purple potato extract	Spermine	79
Di(dihydrocaffeoyl) spermidine	9.4	Purple potato extract	Caffeic acid	79
N^1,N^4,N^{12}-Tris(dihydrocaffeoyl) spermine	18.2	Purple potato extract	Caffeic acid	79
Caffeoyl putrescine	20.4	White potato extract	Spermine	79
Caffeoyl spermine	5.4	White potato extract	Spermine	79
Di(dihydrocaffeoyl) spermidine	101.5	White potato extract	Caffeic acid	79
N^1,N^4,N^{12}-Tris(dihydrocaffeoyl) spermine	29.5	White potato extract	Caffeic acid	79

rye bran (Table 2).[75] Feruloyl putrescine, *p*-coumaroyl spermidine, diferuloyl putrescine, diferuloyl spermidine, diferuloyl spermine, and diferuloyl cadaverine were detected within the seeds (embryo and scutellum) of maize and corn bran (Table 2).[76] These results indicated that the bran of cereal and grain contain a large number of CPAs.

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In addition, CPAs have been identified in *Solanaceae* plants such as tomatoes and Lycium berries.[77] Fifteen conjugated spermidines (Lycibarbar spermidines A−O) were only observed in Lycium berries.[77] These compounds exhibit a distinctive structural characteristic: spermidine is linked to hydroxycinnamic acid and subsequently conjugated with hexoside. Similarly in barley, agmatine conjugated with hexoside has also been discovered, for example, *p*-coumaroyl agmatine hexoside, feruloyl agmatine hexoside, and sinapoyl agmatine hexoside.[71,77] Apart from the reported presence of CPAs in tomatoes, potato, and barley, this type of CPA was uncommonly found in other vegetables.

Due to the lack of commercial reference standards, quantifying CPAs in foods remains formidably challenging, and it is difficult to determine which CPAs are predominant in foods. The hydroxycinnamic acid or polyamine moiety is frequently employed as calibration standards to quantify CPAs (Table 3). For instance, in the Shakya's study,[78] 7 CPAs in potatoes were measured with concentrations from 22 to 280 mg/kg of dry weight, using dihydrocaffeic acid equivalents at 210 nm (Table 3). In the analysis of potatoes, the quantities of caffeoyl putrescine and caffeoyl spermine were quantified as 72.9 and 2.8 g/kg of dry potato extract in purple potato and 20.4 and 5.4 g/kg of dry potato extract in white potatoes, utilizing spermine as the standard[79] (Table 3). Through the isolation and purification of the CPAs in *Lycium barbarum*, the combined content of the 15 CPAs (lycibarbarspermidines A−O) was estimated to exceed 2.1 mg/g, with lycibarbarspermidine A and lycibarbarspermidine F individually surpassing 0.5 mg/g in terms of content[77] (Table 3). Recent studies prepared the 10 CPAs standards (di-*p*-coumaroyl putrescine, tri-*p*-coumaroyl spermidine, dihydroxyferuloyl feruloyl spermidine, tetra-*p*-coumaroyl spermine, tetracaffeoyl spermine, di-*p*-coumaroyl spermidine, *p*-coumaroyl caffeoyl putrescin, di-*p*-coumaroyl-diacetyl spermine, tricaffeoyl spermidine, and di-*p*-coumaroyl-feruloyl spermidine) using preparative HPLC for the quantification of CPAs in 20 types of monofloral bee pollen[11] (Table 3). The levels of 31 CPAs in 20 types of bee pollen ranged from 1.50 to 39.02 mg/g; noteworthily, the levels of CPAs in 11 types of bee pollen constituted more than 1% of the total weight. The highest levels were presented in rose pollen at 39.02 mg/g, followed by pear pollen at 27.58 mg/g and apricot pollen at 22.24 mg/g[11] (Table 3). Among CPAs, conjugated spermidine presented a higher level than that of conjugated putrescine and spermine. Tri-*p*-coumaroyl spermidine existed at a higher level than others, accounting for more than 10 mg/g in 7 types of bee pollen. Pear bee pollen had the highest levels of tri-*p*-coumaroyl spermidine at 26.89 mg/g. The contents of di-*p*-coumaroyl-caffeoyl spermidine and dihydroxy feruloyl-feruloyl spermidine reached 26.17 mg/g in rose bee pollen and 13.2 mg/g in rhus chinensis bee pollen, respectively.[11] These results indicate that bee pollen seems to be the most abundant CPAs source among known natural products. Therefore, bee pollen can be regarded as "a treasure trove of CPAs."

4. FUNCTIONAL PROPERTIES OF POLYAMINES

4.1. Free Polyamines. The functions of FPAs include cell differentiation, cell proliferation, gene regulation, cell signaling, and apoptosis.[80−82] Moreover, since 2009, studies have indicated that polyamines contribute to elongating the healthy life span of animals by activating autophagy and have been implicated in protecting against several age-related diseases, such as safeguarding the kidneys and liver, enhancing cognitive function, and impeding the advancement of heart diseases.[83,84] Elevated levels of polyamines, achieved through increased dietary consumption, have consistently demonstrated a connection with enhanced well-being and decreased overall mortality.[10] FPAs engage extensively with cellular molecules and fulfill various vital bodily roles (Figure 3).

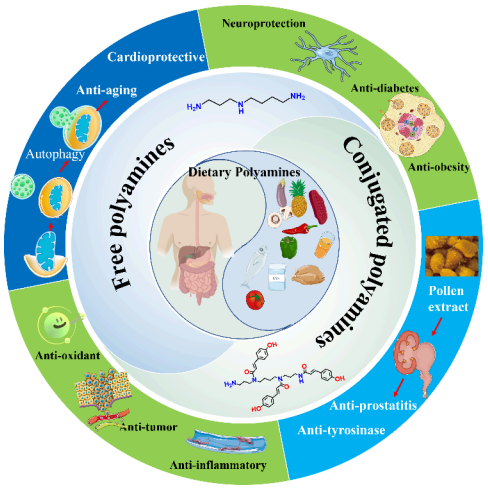

Figure 3. Health benefits of dietary polyamines for the human.

4.1.1. Antiaging. In recent years, research has unveiled polyamines' capacity to stimulate cytoprotective macroautophagy/autophagy, thereby exerting antiaging effects.[9,85,86] This revelation has propelled polyamine dietary supplements to the forefront of the market. The exogenous supply of millimolar spermidine concentrations can significantly prolong the life span of several model organisms, including yeast, *Caenorhabditis elegans*, and *Drosophila melanogaster*.[9,85,86] Spermidine inhibits histone acetyltransferases like Iki3p and Sas3p, reducing histone H3 acetylation and potentially influencing the acetylation of other proteins, thereby upregulating autophagy-related genes.[9] Previous research has indicated that the life-extending effect of spermidine on yeast, nematodes, and flies is nullified when autophagy is inhibited through the deletion of crucial autophagy-related genes, such as *ATG5, ATG6* (known as bec-1 in *C.* elegans), or *ATG7*.[9] These findings underscore the indispensable role of autophagy induction in spermidine's antiaging mechanism. In animal models, feeding polyamine (spermine 374 nmol/g and spermidine 1540 nmol/g) to mice can significantly increase their survival rate and decrease the expression of a senescence marker protein in both kidney and liver.[87] Adding probiotic bifidobacteria that produce polyamines, individually or in conjunction with the polyamine precursor arginine, elevates the spermidine and spermine levels in blood.[88] This supplementation also results in reducing mortality rates and the occurrence of skin-related disorders in aged mice.

In humans, spermidine levels significantly decline with aging, and a possible connection between reduced endogenous spermidine concentrations and age-related deterioration has been suggested.[9,85,86] In clinical trials, the prospective Bruneck Study utilized 20 years of detailed dietary assessments involving 829 participants (aged 45−84), with 341 deaths occurring between 1995 and 2015.[89] This study linked the elevated dietary spermidine intake to reduced mortality,

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particularly in vascular, cancer, or other-cause deaths, and fatal heart failure.[89] The observed correlation remained significant even after adjusting for potential confounding variables like alcohol consumption, diet quality, physical activity, and socioeconomic status. In the Bruneck Study,[10] significant spermidine sources intake was identified as whole grains (13.4%), apples and pears (13.3%), green salad (9.8%), vegetable sprouts (7.3%), and potatoes (6.4%). Furthermore, the analysis indicated an age-dependent relationship with spermidine intake: advanced age was associated with reduced consumption. The study also unveiled positive links between spermidine/spermine intake levels and various health aspects, including a lowered risk of cardiovascular disease, and a negative association with general mortality, including cancer-related mortality. In the subsequent SAPHIR Study,[89] a separate cohort of 1,770 healthy participants (663 women and 1,107 men aged 39−67) was investigated from 1999 to 2002, with mortality follow-up until 2013. SAPHIR Study confirmed that a diet rich in spermidine is associated with increased survival, displaying the strongest inverse correlation with mortality among identified macronutrients and micronutrients. This aligns with the declining spermidine (and spermine) during aging.[90] The levels of polyamine among long-lived individuals (nonagenarians and centenarians), like those observed in middle-aged individuals, underscores the potential importance of spermidine and spermine in relation to longevity. Consequently, a diet rich in polyamines has been linked to increased life span, suggesting that replenishing spermidine levels through dietary or pharmacological means is crucial for aging individuals. Thus, a physiological autophagy inducer, spermidine, is hailed as an "anti-aging vitamin" and a novel longevity elixir.[9]

4.1.2. Cardioprotective. Polyamines play a significant role in preventing cardiovascular diseases. An increased spermidine intake can reduce the occurrence of cardiovascular diseases, high blood pressure, and heart failure.[86] The administration of natural polyamine spermidine through oral supplementation has shown cardioprotective effects characterized by the attenuation of cardiac hypertrophy and the preservation of diastolic function in aged mice.[10] A 6-week supplementation of spermine and spermidine in mice also reversed age-related alterations in myocardial fibrosis and hindered cellular apoptosis within the heart.[91] Notably, in Dahl salt-sensitive rats subjected to a high-salt diet (a model for hypertension-induced congestive heart failure), spermidine intake led to reducing systemic blood pressure, enhancing titin phosphorylation, preventing cardiac hypertrophy, and declining diastolic function, consequently impeding the progression toward heart failure.[10] Spermidine supplementation demonstrated the augmentation of cardiac autophagy, mitophagy, and mitochondrial respiration, accompanied by enhanced mechanical and elastic properties *in vivo*.[10] This coincided with increased titin phosphorylation and the attenuation of subclinical inflammation. However, the conferred cardioprotection by spermidine supplementation was abolished in mice lacking the autophagy-related protein Atg5 in cardiomyocytes.[10] Research also suggests that the preventative effects of polyamines against cardiovascular diseases are interconnected with their anti-inflammatory properties.[92] This anti-inflammatory role of polyamines in cardiovascular patients bears similarities to that of polyunsaturated fatty acids (PUFA 3-n) and statins.[92,93] In human subjects, a higher dietary intake of spermidine, as assessed through dietary questionnaires, correlates with decreased blood pressure and a reduced occurrence of cardiovascular disease.[10] Furthermore, previous research collected age-standardized mortality rates and pertinent data concerning individuals with cardiovascular disease from the World Health Organization and the International Monetary Fund across 48 diverse European and other Western nations.[93] The findings reveal an inverse relationship between dietary polyamines and the mortality rate attributed to cardiovascular diseases.[93]

4.1.3. Antitumor. Polyamines play a crucial role in facilitating cellular proliferation and growth. The disruption of polyamine metabolism stands as a distinctive hallmark across various tumor categories. Elevated levels of polyamines, resulting from augmented biosynthesis, manifest prominently in malignancies such as skin, breast, colon, lung, and prostate cancers.[94] Perturbations in polyamine biosynthesis pathways, predominantly attributed to escalated decarboxylase (ODC), engender heightened intracellular polyamine accumulation within cancerous cells.[95] Endeavors have been undertaken to mitigate polyamine biosynthesis by obstructing ornithine decarboxylase (ODC) activity, with moderate success in non-Hodgkin's lymphoma.[94] In recent years, efforts have addressed cancer by decreasing heightened polyamine levels within cancer cells.[96] Endeavors to combat cancer by reducing intracellular polyamine levels represent a strategy to counteract the growth-promoting impacts of polyamines.[3] Notably, current research has achieved consensus that healthy individuals' polyamine intake does not increase cancer incidence.[3]

On the contrary, multiple studies have indicated that dietary supplementation of spermidine can reduce the occurrence of tumors.[97−99] Dietary administration of spermidine has been observed to alleviate the severity of hepatic fibrosis and mitigate the occurrence of hepatocellular carcinomas triggered by chemical insults in murine models.[99] Augmented consumption of dietary polyamines, facilitated through chow enriched with spermidine, spermine, and putrescine, has been shown to induce a temporal lag in chemically induced tumorigenesis among juvenile BALB/c male mice.[97] Supplementation of spermidine has been demonstrated to curtail the growth of transplantable tumors in mice subjected to chemotherapeutic regimens. This effect of spermidine is a phenomenon shared by other caloric restriction mimetics (CRMs),[98] as well as by fasting or hypocaloric dietary interventions.[100] It is underpinned by the facilitation of immunosurveillance mechanisms. Furthermore, oral supplementation of polyamine-producing probiotic bacteria has lowered the frequency of visible skin tumors in aging Crj:CD-1 female mice.[101]

4.1.4. Anti-inflammatory. Dietary spermidine and spermine inhibit the release of proinflammatory cytokines across various pathological contexts. These properties are mainly attributed to autophagy induction, which possesses anti-inflammatory properties due to its role in restraining inflammasome activation.[102] Ingested spermidine counters the age-related rise in plasma levels of cytokines like tumor necrosis factor-alpha (TNF-α) in mice[103] and also protects against fatal sepsis.[104] Moreover, lymphocyte function-associated antigen-1 (LFA-1) is vital for immune cell interactions, and its levels rise with age in blood cells.[105] Oral spermidine and spermine reduce LFA-1 expression in aging male mice and human lymphocytes, possibly through changes in DNA methylation associated with aging or by inhibiting inflammatory factors like

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NF-κB in immune cells.[106] Previous research has reviewed that spermidine can significantly reduce the expression of inflammatory factors induced by LPS in BV2 cells, including NO, PGE2, TNF-α, and IL-6, by the inhibition of the NF-κB pathway due to suppression of PI3K/AKT and MAPK signaling pathways.[107] Spermine has also been reported to inhibit the synthesis of the proinflammatory cytokines (TNF, IL-1, IL-6, MIP-1 a, and MIP-1 b) induced by LPS.[105] Notably, when spermine was locally administered *in vivo*, it demonstrated a protective effect in mice, mitigating the development of acute footpad inflammation induced by carrageenan.[108] These findings suggest that polyamines may exert anti-inflammatory effects through multiple mechanisms.

4.1.5. Antidiabetes and Antiobesity. Polyamines present significant potential for treating obesity and type 2 diabetes, making them a crucial topic for future research. Administering spermine daily to mice on a high-fat diet (HFD) prevented adiposity and enhanced glucose tolerance.[109] In mouse models, spermidine or spermine has effectively improved glucose homeostasis, insulin sensitivity, and decreased adiposity and hepatic fat buildup.[110] These properties are mainly attributed to polyamine metabolism related to NAD+ metabolism and Sirtuin signaling, which play a crucial role in energy metabolism processes.[109] Additionally, agmatine demonstrates favorable effects in addressing metabolic disorders.[111] Agmatine can elicit insulin secretion from pancreatic β-islet cells by inhibiting K_{ATP} channels.[111] Agmatine exerts an antihyperglycemic effect by facilitating glucose uptake in muscle and inhibiting gluconeogenesis in the liver, achieved through the augmented secretion of β-endorphin. The supplementation of agmatine exerts notable influences on glucose metabolism within obese models.[110] Moreover, polyamines can resist obesity caused by an HFD diet by activating autophagy.[112] It is important to mention that autophagy is essential for achieving complete weight loss during acute starvation. It serves as a countermeasure against weight gain and obesity-related issues in mice with hypercaloric diets.[112] On the other hand, the primary pathogenic cause of diabetic complications is the accumulation of tissue advanced glycation end products (AGEs). Polyamines can act as antiglycan agents to slow the formation of AGEs.[110] This outcome can be attributed to the interaction involving the unbound amino groups of polyamines and the exceptionally reactive carbonyl compounds. Investigations *in vitro* have displayed that the cellular nucleus's millimolar spermine concentrations can shield DNA and histones against glycation.[113] Additional research elucidates the involvement of polyamines in diabetes and defines appropriate polyamine intake according to safety guidelines for individuals with diabetes.

4.1.6. Scavenging Free Radical and Antioxidant. Polyamines, such as spermine, spermidine, putrescine, and agmatine have been studied for their potential free radical scavenging properties. Polyamines' free radical scavenging activity is attributed to their chemical structure, which allows them to neutralize reactive species through various mechanisms, including electron donation and metal ion chelation. Moreover, polyamines can upregulate the expression of different antioxidant enzymes, like catalase and glutathione, and eliminate free radicals in the body.[114] Additionally, previous research demonstrated that polyamines, especially spermine, can act directly as a free radical scavenger. Spermine reacts with hydroxyl radicals to generate bis-α-1-(N,N-dihydroxy) amino-12-(N,N-dihydroxy) amino-4,9-dodecane, which subsequently leads to the formation of 1,12-bis-1,12-di(hydroxyimino)-4,9-dodecane, ultimately resulting in the production of 1,12- bis-1,12-dioxo-4,9-dodecane.[115] Previous studies have reviewed that all polyamines can offer protection against oxidative stress caused by various pathological conditions, such as hypoxia,[116] ischemia,[117] and inflammation.[118] Polyamines reduced the production of superoxide in the NADH/phenazine methosulfate reaction and exhibited approximately 20 times more effectiveness in neutralizing H_2O_2 than the antioxidants (Trolox, thiourea).[119] Spermine and spermidine demonstrated free radical scavenging capacity dependent on their concentration in foods. The ability of polyamines to scavenge free radicals bestows upon them formidable antioxidant prowess. The antioxidative impact across a broad concentration spectrum, ranging from 30 to 1,250 μg/mL.[120] Notably, the more amino groups have the higher antioxidant capacity, with spermine being the most potent.[2] Similarly, agmatine stands out for its ability to act as a free radical scavenger, thereby providing a cytoprotective effect. This effect is achieved by safeguarding mitochondria against oxidative stresses, ultimately reducing the occurrence of apoptotic cell death.[111]

It is important to note that while polyamines possess antioxidant properties, their overall impact can vary depending on cellular context and concentration. In some cases, excessively high levels of polyamines might even contribute to oxidative stress. Therefore, the role of polyamines in antioxidant defense is complex and requires further investigation.

4.1.7. Neuroprotective. Evidence suggests that polyamines, particularly spermidine and spermine, have neuroprotective properties. These polyamines protect from neurodegeneration through autophagy, ion channels, neurotransmitter receptors, and various signaling pathways.[121] Polyamines can regulate autophagy, a cellular process responsible for clearing damaged proteins and organelles. Dysregulation of autophagy is often seen in neurodegenerative diseases.[121] Polyamines can help reduce oxidative stress within neurons, which significantly contributes to neurodegeneration.[121] This may be attributed to the free radical scavenging and regulation of antioxidant enzyme activity. Polyamines have been linked to suppressing neuroinflammation, a common feature in many neurodegenerative disorders.[2,3] By modulating inflammatory responses, polyamines might contribute to neuroprotection. Proper regulation of calcium ions is critical for neuronal function. Polyamines can influence calcium channels, help maintain appropriate calcium levels, and prevent excitotoxicity, which is the excessive activation of neurons due to high calcium levels.[2,3] In flies, dietary spermidine guards against age-related memory decline[10,14] and loss of movement[122] via autophagy. In a mouse multiple sclerosis model, oral spermidine supplementation reduces optic nerve and spinal cord demyelination, preserving retinal cells.[106] Spermidine also aids optic nerve recovery after injury[123] and counteracts retinal degeneration in glaucoma.[124] Enhancing colonic polyamines via oral arginine and bifidobacteria boosts aged mice's spatial learning.[103] These findings highlight spermidine's potential neuroprotection against neurodegenerative conditions and motor disorders.

Numerous investigations have documented the therapeutic efficacy of agmatine on diverse neurological disorders, notably encompassing the treatment of conditions such as depression,

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anxiety, neuropathic pain, cognitive and learning impairments, as well as drug dependence.[111,125,126] Agmatine, functioning as a neuromodulator, orchestrates the regulation of multiple neurotransmitters and signaling pathways. Numerous investigations unravel the intricate mechanisms.[111,125,126] This neuroprotection appears to be facilitated through mitigation of oxidative damage, suppression of neuroinflammation, and modulation of proapoptotic signaling.[88,103,104] Moreover, concerning the therapeutic impact of agmatine on neurological diseases with a specific focus on ion channels and receptors, an additional review has been disseminated.[127] Given that these processes are implicated in disorders associated with acute and chronic excitotoxicity, such as ischemia, epilepsy, traumatic brain injury, spinal cord injury, neurodegenerative conditions, and psychiatric disorders, as well as in nociception, agmatine emerges as a promising therapeutic approach for central nervous system disorders.[125] Furthermore, agmatine can stimulate the expression of trophic factors and promote adult neurogenesis, thereby contributing to its efficacy in inducing endogenous repair mechanisms.[125]

4.2. Conjugated Polyamines. The scientific exploration in this field has mainly focused on plants and their reactions to stressors. In recent years, while CPAs in food have been continuously discovered and their health benefits for the human body are continually being updated, there are still limited reports on the bioactivity of these phenolamides (CPAs) in human health (Figure 3).

4.2.1. Antiprostatitis and Antiprostate Hyperplasia. Although limited research reports on the beneficial effects of CPAs on human health, as early as 1959, a medication rich in feruloyl putrescine (Cernilton) produced by a Swedish company had already been introduced to the world. Cernilton is one of two pharmaceutical medications approved globally for effectively addressing chronic prostatitis and prostate hyperplasia.[128] The Japanese health authorities granted registration to Cernilton in 1969 due to its efficacy in treating chronic prostatitis, chronic pelvic pain syndrome, and benign prostate hyperplasia. Cernilton comprises two distinct pollen extract fractions: the water-soluble T60 and the lipid-soluble GBX.[12,129] Emerging evidence indicates that these two fractions trigger specific effects in animal models, including the reduction of inflammation, inhibition of cellular proliferation, and relaxation of smooth muscles.[12,129] Notably, research outcomes have clarified that the primary antiprostatitis and antiprostate hyperplasia effect of the T60 fraction is attributed to feruloyl putrescine.[12] In China, Cernilton, known as Prostate Tablets (a prescription medicine), has a history of 40 years in treating prostate disease. The product label of Prostate Tablets Pharmaceuticals explicitly states that its main ingredient is feruloyl putrescine (γ-feruloyl butyldiamine) at 70 mg per tablet. A mice study has reviewed that feruloyl putrescine inhibited the noradrenaline-induced contraction of urethral strips in a noncompetitive manner, producing 32.5% inhibition at 378 μM.[12] Furthermore, feruloyl cadaverine has also exhibited inhibited urethral contraction activity, producing 46.3 ± 7.1% inhibition at 359 μM.[12] The therapeutic effects of other CPAs on prostate diseases will be a focal point of future research.

4.2.2. Anti-inflammatory. CPAs extracted from bee pollen can significantly reduce the expression of NO and COX-2 and the levels of TNF-α, IL-1β, and IL-6 in LPS-induced macrophages, and this effect is concentration-dependent.[130] Several experimental studies indicate that kukoamine B (N^1,N^{10}-bis-dihydrocaffeoyl spermine) possesses potential anti-inflammatory effects for sepsis treatment.[131,132] Liu et al. identified kukoamine B as a novel dual inhibitor against LPS and CpG DNA, pivotal molecules inducing sepsis, thereby suggesting its potential candidacy for sepsis treatment, in contrast to the current drugs that target either LPS or CpG DNA.[131,132] Another study found that kukoamine B can bind to LPS, hastening its blood clearance through the asialoglycoprotein receptor.[133] Their research suggested that kukoamine B enhances hepatocyte LPS uptake, even in TLR4−/− mice, possibly by upregulating the asialoglycoprotein receptor expression.

4.2.3. Antidiabetes. Kukoamines A and B have also been reported to possess antidiabetic activity. In a mouse model of type II diabetes,[134] kukoamine B was observed to mitigate symptoms associated with diabetes by influencing nuclear transcription factors (such as NF-κB and/or PPAR) to modify lipid metabolism and decrease persistent inflammation. Notably, kukoamine B demonstrated a more extraordinary ability to regulate lipid metabolism, enhance fatty oxidation, and impact anti-inflammatory indicators than metformin.[134] Subsequent research elucidated that kukoamines A and B exhibited a discernible dose-dependent impediment against the aggregation of hIAPP, a pivotal constituent implicated in the proteinaceous deposits localized within the islets of Langerhans in patients afflicted with non-insulin-dependent diabetes mellitus.[135] This observation underscores the prospective utility of kukoamines A (N^1,N^{14}-bis-dihydrocaffeoyl spermine) and B as agents that can forestall and address type 2 diabetes mellitus.[135] In a murine model subjected to a high-fat dietary regimen, it was ascertained that the administration of kukoamine A engendered a reduction in hepatic histological damage, mitigated hepatic triglyceride levels, and decreased serum aspartate transaminase and alanine transaminase activities.[136] Furthermore, kukoamine A treatment was associated with the attenuation of elevated fasting blood glucose and insulin concentrations, as well as reduced serum levels of proinflammatory cytokines such as TNF-α, IL-1β, and iIL-6, along with diminished C-reactive protein levels.[136] Therefore, kukoamine A can mitigate high-fat-diet-induced insulin resistance and fatty liver disease *in vivo*.

Moreover, Zhang et al. investigated the effect of phenolamide extract from apricot bee pollen on obese mice fed a high-fat diet (HFD).[17] The results demonstrate that apricot bee pollen extract containing 87.75% CPAs (tri-*p*-coumaroyl spermidine as the dominant compound) exhibits the capacity to significantly decrease hepatic and epididymal fat lipid accumulation, enhance glucose tolerance, mitigate insulin resistance, and ameliorate lipid metabolism in mice subjected to a high-fat diet (HFD).

4.2.4. Antityrosinase. Previous research has evaluated the tyrosinase inhibitory activity of three putrescine-conjugated CPAs (N,N′-dicoumaroyl-putrescine, N-*p*-coumaroyl-N′-feruloyl putrescine, and N,N′-diferuloyl-putrescine) isolated from corn bran using mushroom tyrosinase.[137] It was found that these three CPAs all exhibited tyrosinase inhibitory activity, especially N,N′-dicoumaroyl-putrescine (IC_{50} = 181.73 μM), presenting the best performance.[138] To comprehensively elucidate the chemical components of bee pollen that inhibit tyrosinase, the researchers evaluated the antityrosinase activity of bee pollen extract (BPE) from eight species.[13] The findings indicated significant differences in the antityrosinase activity among the eight BPEs, with IC_{50} values ranging from 10.08 to

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408.81 μg/mL.[13] The 26 CPAs consisting of 21 spermidine derivatives and 5 spermine derivatives exhibited exceptionally high correlations with the antityrosinase activity.[13] Eighteen CPAs from bee pollen of *Quercus mongolica* can inhibit mushroom tyrosinase as an *in vitro* assay system.[52] Spermidine-conjugated coumaroyl and caffeoyl showed tyrosinase inhibition with IC_{50} values of 18.9 to 85.8 μM.[52] Adding methoxyl moiety to phenolic groups reduced the inhibitory activity, comprising methoxycoumaroyl and methoxybenzoyl moieties with IC_{50} values of >100 μM.[52] Moreover, this study also suggested that the inhibitory activity of spermidines was better with *trans*-coumaroyl than with *cis*-coumaroyl moieties.[52] Concerning BPA structures, the most potent tyrosinase inhibition was observed in spermidine carrying four coumaroyl groups, followed by spermidines containing three phenolic groups and putrescine derivatives with two phenolic groups.[52] The tyrosinase enzyme reaction is the rate-limiting step in melanin synthesis, which plays a crucial role in preventing melanin accumulation. Thus, CPAs can be used in functional whitening cosmetics.

4.2.5. Neuroprotective. Several studies have reviewed that kukoamines A and B possess a neuroprotective effect. Hu reported that kukoamine A exhibited strong neuroprotective effects through antioxidative stress, anti-inflammation, and antiexcitotoxicity mechanisms.[139] Oxidative stress and overactivation of N-methyl-D-aspartate receptors (NMDARs) are pivotal contributors to brain injury, and kukoamine A has been identified as being capable of inhibiting NMDARs using a confirmed molecular docking mechanism.[139] In oxidatively stressed cells induced by H_2O_2, kukoamine A demonstrated the attenuation of cellular apoptosis induction, suppression of lactate dehydrogenase levels, production of reactive oxygen species, decrease in malondialdehyde levels, mitigation of matrix metalloproteinase loss, reduction of intracellular Ca^{2+} overload induced by NMDA, and enhancement of superoxide dismutase activity. These collective findings underscore kukoamine A's neuroprotective efficacy, attributed to its dual role in mitigating oxidative stress and inhibiting N-methyl-D-aspartate receptors in SHSY5Y cells.[140] Kukoamine A demonstrated a neuroprotective effect on a neurotoxin-induced Parkinson's model through apoptosis inhibition and autophagy enhancement. Additionally, via antioxidant and inactivation of the apoptosis pathway, kukoamine A has a neuroprotective effect against cerebral ischemia.[137,141] In a mouse study, male Wistar rats exposed to whole-brain irradiation received immediate intravenous injections of kukoamine A or a control solution.[142] The results indicated that kukoamine A, administered at 10 and 20 mg/kg doses, effectively reduced neuronal damage caused by irradiation through antioxidative and antiapoptotic mechanisms.[142] Furthermore, Zhang et al. discovered that kukoamine A can hinder radiation-induced neuroinflammation and safeguard hippocampal neurogenesis in rats by suppressing the activation of NF-κB and AP-1.[143] In conclusion, the neuroprotective activity of kukoamine A represents a significant avenue of benefit to human health from CPAs.

4.2.6. Others. Research conducted both *in vitro* and *in vivo* has shown that kukoamine A can inhibit the growth and migration of human glioblastoma cells.[144] *In vitro*, kukoamine A can induce cell apoptosis, arrest the cell cycle at the G0/G1 phase, and inhibit the migration and invasion of glioblastoma cells. *In vivo*, administering kukoamine A at 10, 20, and 40 mg/kg to tumor-bearing mice significantly inhibits the growth of glioblastoma cells.[144]

It has been confirmed that tri-*p*-coumaroyl spermidine isolated from *Artemisia caruifolia* can inhibit HIV-1 protease.[145] Tetra-*p*-coumaroyl spermine and penta-*p*-coumaroyl tetraethylenepentamine, which possess longer chains, exhibited greater potency as inhibitors of HIV-1 protease in comparison to tri-*p*-coumaroyl spermidine.[145] Notably, neither FPAs nor *p*-coumaric acid exhibit inhibitory activity against HIV-1 protease. These results indicated that CPAs offer distinct health advantages over their parent phenolic acids and amines.

Mude et al.[146] have prepared four CPAs, including caffeoyl spermidine, dicaffeoyl spermidine, caffeoyl spermine, and dicaffeoyl spermine, by varying the caffeic acid to polyamines. The obtained CPAs demonstrated superior antioxidant activity compared to that of the caffeic acid. CPAs displayed notable antibacterial efficacy against *E. coli* and *S. aureus* under their respective natural pH conditions. Furthermore, these compounds showed remarkable anticancer properties against HeLa cells, even at submillimolar concentrations, under native and pH 7.5 conditions.[146] Zhang and colleagues[147] compared the antioxidant activity of flavonoid compounds and CPAs in rapeseed bee pollen. The research revealed that the antioxidant activity of CPAs surpassed that of flavonoids. Furthermore, CPAs demonstrated more effective protective effects on AAPH-induced injury to HepG2 cells than flavonoids. Additionally, CPAs were observed to significantly reduce levels of reactive oxygen species, alanine aminotransferase, and aspartate aminotransferase while simultaneously increasing superoxide dismutase and glutathione levels.[147]

There is relatively limited research concerning the modulation of gut microbiota by CPAs. Recently, research indicated that CPAs (especially tri-*p*-coumaroyl spermidine) from apricot bee pollen can counteract the elevation in the *Firmicutes/Bacteroidetes* ratio observed in mice fed an HFD.[17] Furthermore, CPAs promoted the proliferation of beneficial bacteria like *Muribaculaceae* and *Parabacteroides* while concurrently diminishing the presence of detrimental bacteria such as *Peptostreptococcaceae* and *Romboutsia*.[17] This indicates that CPAs can regulate gut microbiota, a potentially pivotal avenue for research into the function of CPAs.

5. CONCLUSION AND PERSPECTIVES

Dietary polyamines are present in various foods, including animal, plant, and microbial sources, with free or conjugated forms, and their content and distribution vary depending on the type of food. Dietary polyamines possess various functions for human health, especially in antiaging and treating prostate diseases. Despite the considerable attention on CPAs in recent years and with new CPAs being continually discovered, detecting and characterizing CPAs in food remains an ongoing research frontier due to their complexity and underlying functional roles. As a significant class of natural compounds, we speculate that the future prospects of CPAs in their physiological applications are expected to surpass those of flavonoids, phenolic acids, and terpenoids. To better harness the benefits of dietary polyamines, the following key points should be addressed in the future. First, although *in vitro* and *in vivo* studies have demonstrated that spermidine can exert significant antiaging effects by activating autophagy, dietary supplements containing spermidine have gained popularity and are being sold worldwide, clinical research results are still limited. It is necessary to expedite progress in clinical research

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to benefit humanity sooner. Second, the structural diversity yields thousands of CPAs, but only a few dozen have been identified in foods, posing challenges in quantification due to limited commercial standards and hindering the estimation of daily phenolamide intake in foods. Novel techniques with higher sensitivity, resolution, and accuracy will be necessary to locate CPAs in foods, while expediting the isolation and purification of high-purity CPAs. Fostering commercial standards is essential. Third, there is a dearth of research on the potential health benefits of CPAs in human physiology, and the multifarious therapeutic attributes of CPAs remain largely unexplored. It underscores the need for future studies to elucidate the medicinal properties of CPAs, especially in prostatitis and prostate enlargement, and to explore their applications in functional food development and personalized nutrition strategies. Fourthly, the effect of fermentation and microorganisms on the CPA profile, as well as the changes in polyamines during the culinary process, should be given particular consideration in future research. Finally, the toxicological evaluation of dietary polyamines, the content limitations, and legal requirements within food constitute imperative prerequisites for the enhanced application of dietary polyamines in the future.

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Notes

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REFERENCES

(1) Bachrach, U. The early history of polyamine research. *Plant Physiology and Biochemistry* **2010**, *48* (7), 490−495.

(2) Muñoz-Esparza, N. C.; Latorre-Moratalla, M. L.; Comas-Basté, O.; Toro-Funes, N.; Veciana-Nogués, M. T.; Vidal-Carou, M. C. Polyamines in food. *Frontiers in nutrition* **2019**, *6*, 108.

(3) Hirano, R.; Shirasawa, H.; Kurihara, S. Health-promoting effects of dietary polyamines. *Medical Sciences* **2021**, *9* (1), 8.

(4) Larqué, E.; Sabater-Molina, M.; Zamora, S. Biological significance of dietary polyamines. *Nutrition* **2007**, *23* (1), 87−95.

(5) Muñoz-Esparza, N. C.; Comas-Basté, O.; Vásquez-Garibay, E. M.; Veciana-Nogués, M. T.; Latorre-Moratalla, M. L.; Vidal-Carou, M. C. Polyamines in Human Milk and Their Benefits for Infant Health. *Infant Nutrition and Feeding*; IntechOpen: 2023. DOI: 10.5772/intechopen.110868

(6) Wang, W.; Snooks, H. D.; Sang, S. The chemistry and health benefits of dietary phenolamides. *Journal of agricultural and food chemistry* **2020**, *68* (23), 6248−6267.

(7) Roumani, M.; Besseau, S.; Gagneul, D.; Robin, C.; Larbat, R. Phenolamides in plants: An update on their function, regulation, and origin of their biosynthetic enzymes. *Journal of Experimental Botany* **2021**, *72* (7), 2334−2355.

(8) Li, Z.; Zhao, C.; Zhao, X.; Xia, Y.; Sun, X.; Xie, W.; Ye, Y.; Lu, X.; Xu, G. Deep annotation of hydroxycinnamic acid amides in plants based on ultra-high-performance liquid chromatography-high-resolution mass spectrometry and its in silico database. *Analytical chemistry* **2018**, *90* (24), 14321−14330.

(9) Madeo, F.; Bauer, M. A.; Carmona-Gutierrez, D.; Kroemer, G. Spermidine: a physiological autophagy inducer acting as an anti-aging vitamin in humans? *Autophagy* **2019**, *15* (1), 165−168.

(10) Madeo, F.; Hofer, S. J.; Pendl, T.; Bauer, M. A.; Eisenberg, T.; Carmona-Gutierrez, D.; Kroemer, G. Nutritional aspects of spermidine. *Annual review of nutrition* **2020**, *40*, 135−159.

(11) Qiao, J.; Feng, Z.; Zhang, Y.; Xiao, X.; Dong, J.; Haubruge, E.; Zhang, H. Phenolamide and flavonoid glycoside profiles of 20 types of monofloral bee pollen. *Food Chem.* **2023**, *405*, 134800.

(12) NAKASE, K.; KIMURA, I.; KIMURA, M. Effects of pollen-extract components, diamines and derivatives of feruloylputrescine on isolated bladder and urethral smooth muscles of mice. *Japanese Journal of Pharmacology* **1990**, *53* (2), 157−164.

(13) Zhang, X.; Yu, M.; Zhu, X.; Liu, R.; Lu, Q. Metabolomics reveals that phenolamides are the main chemical components contributing to the anti-tyrosinase activity of bee pollen. *Food Chem.* **2022**, *389*, 133071.

(14) Alcázar, R.; Fortes, A. M.; Tiburcio, A. F. Polyamines in plant biotechnology, food nutrition, and human health. Frontiers Media SA: 2020; Vol. *11*, p 120.

(15) Muñoz-Esparza, N. C.; Comas-Basté, O.; Latorre-Moratalla, M. L.; Veciana-Nogués, M. T.; Vidal-Carou, M. C. Differences in polyamine content between human milk and infant formulas. *Foods* **2021**, *10* (11), 2866.
(16) Liu, H.; Liu, Y.; Han, H.; Lu, C.; Chen, H.; Chai, Y. Identification and characterization of phenolamides in tea (Camellia sinensis) flowers using ultra-high-performance liquid chromatography/Q-Exactive orbitrap mass spectrometry. *Food Chem.* **2023**, *424*, 136402.
(17) Zhang, X.; Wu, X.; Xiao, G.; Liu, G.; Dong, H.; Liu, R.; Lu, Q. Phenolamide extract of apricot bee pollen alleviates glucolipid metabolic disorders and modulates the gut microbiota and metabolites in high-fat diet-induced obese mice. *Food & Function* **2023**, *14* (10), 4662−4680.
(18) Hou, Y.; He, W.; Hu, S.; Wu, G. Composition of polyamines and amino acids in plant-source foods for human consumption. *Amino Acids* **2019**, *51*, 1153−1165.
(19) Veeranagamallaiah, G.; Sudhakar, C. Determination of polyamines by dansylation, benzoylation, and capillary electrophoresis. *Plant Stress Tolerance: Methods and Protocols* **2017**, *1631*, 313−323.
(20) Yu, Z.; Huang, H.; Zhang, H.; Kessler, B. M. Improved profiling of polyamines using two-dimensional gas chromatography mass spectrometry. *Talanta* **2019**, *199*, 184−188.
(21) DeFelice, B. C.; Fiehn, O. Rapid LC-MS/MS quantification of cancer related acetylated polyamines in human biofluids. *Talanta* **2019**, *196*, 415−419.
(22) Baratella, D.; Bonaiuto, E.; Magro, M.; de Almeida Roger, J.; Kanamori, Y.; Lima, G. P. P.; Agostinelli, E.; Vianello, F. Endogenous and food-derived polyamines: determination by electrochemical sensing. *Amino Acids* **2018**, *50*, 1187−1203.
(23) Kalač, P.; Křižek, M.; Pelikánová, T.; Langová, M.; Veškrna, O. Contents of polyamines in selected foods. *Food Chem.* **2005**, *90* (4), 561−564.
(24) Cipolla, B.; Havouis, R.; Moulinoux, J.-P. Polyamine contents in current foods: a basis for polyamine reduced diet and a study of its long term observance and tolerance in prostate carcinoma patients. *Amino acids* **2007**, *33*, 203−212.
(25) Nishibori, N.; Fujihara, S.; Akatuki, T. Amounts of polyamines in foods in Japan and intake by Japanese. *Food Chem.* **2007**, *100* (2), 491−497.
(26) Dadáková, E.; Pelikánová, T.; Kalač, P. Content of biogenic amines and polyamines in some species of European wild-growing edible mushrooms. *European Food Research and Technology* **2009**, *230*, 163−171.
(27) Galgano, F.; Caruso, M.; Condelli, N.; Favati, F. Focused review: agmatine in fermented foods. *Frontiers in Microbiology* **2012**, *3*, 199.
(28) Toro-Funes, N.; Bosch-Fuste, J.; Latorre-Moratalla, M.; Veciana-Nogués, M.; Vidal-Carou, M. Biologically active amines in fermented and non-fermented commercial soybean products from the Spanish market. *Food Chem.* **2015**, *173*, 1119−1124.
(29) Kralj Cigić, I.; Rupnik, S.; Rijavec, T.; Poklar Ulrih, N.; Cigić, B. Accumulation of agmatine, spermidine, and spermine in sprouts and microgreens of alfalfa, fenugreek, lentil, and daikon radish. *Foods* **2020**, *9* (5), 547.
(30) Eliassen, K. A.; Reistad, R.; Risøen, U.; Rønning, H. F. Dietary polyamines. *Food Chem.* **2002**, *78* (3), 273−280.
(31) Santos, W. C.; Souza, M. R.; Cerqueira, M. M.; Glória, M. B. A. Bioactive amines formation in milk by Lactococcus in the presence or not of rennet and NaCl at 20 and 32 C. *Food chemistry* **2003**, *81* (4), 595−606.
(32) Nishimura, K.; Shiina, R.; Kashiwagi, K.; Igarashi, K. Decrease in polyamines with aging and their ingestion from food and drink. *Journal of biochemistry* **2006**, *139* (1), 81−90.
(33) Saaid, M.; Saad, B.; Hashim, N. H.; Ali, A. S. M.; Saleh, M. I. Determination of biogenic amines in selected Malaysian food. *Food Chem.* **2009**, *113* (4), 1356−1362.
(34) Determination of biogenic amines in fruit, vegetables, and chocolate using ion chromatography with suppressed conductivity and integrated pulsed amperometric detections. *Application Update 162*; Dionex: 2016.
(35) Muñoz-Esparza, N. C.; Costa-Catala, J.; Comas-Basté, O.; Toro-Funes, N.; Latorre-Moratalla, M. L.; Veciana-Nogués, M. T.; Vidal-Carou, M. C. Occurrence of polyamines in foods and the influence of cooking processes. *Foods* **2021**, *10* (8), 1752.
(36) Soda, K.; Phan Nguyen Thanh Binh; Masanobu Kawakami. Mediterranean diet and polyamine intake: possible contribution of increased polyamine intake to inhibition of age-associated disease. *Nutrition and Dietary Supplements* **2010**, 1−7.
(37) Okamoto, A.; Sugi, E.; Koizumi, Y.; Yanagida, F.; Udaka, S. Polyamine content of ordinary foodstuffs and various fermented foods. *Biosci., Biotechnol., Biochem.* **1997**, *61* (9), 1582−1584.
(38) Miguélez-Arrizado, M. J.; Bover-Cid, S.; Latorre-Moratalla, M. L.; Vidal-Carou, M. C. Biogenic amines in Spanish fermented sausages as a function of diameter and artisanal or industrial origin. *Journal of the Science of Food and Agriculture* **2006**, *86* (4), 549−557.
(39) Bashiry, M.; Hoseini, H.; Mohammadi, A.; Sadeghi, E.; Karimian-Khosroshahi, N.; Barba, F. J.; Mousavi Khaneghah, A. Industrial and culinary practice effects on biologically active polyamines level in Turkey meat. *Quality Assurance and Safety of Crops & Foods* **2021**, *13* (2), 67−78.
(40) Lian, J.; Liang, Y.; Zhang, H.; Lan, M.; Ye, Z.; Lin, B.; Qiu, X.; Zeng, J. The role of polyamine metabolism in remodeling immune responses and blocking therapy within the tumor immune microenvironment. *Frontiers in Immunology* **2022**, *13*, 912279.
(41) Muñoz-Esparza, N. C.; Vásquez-Garibay, E. M.; Guzmán-Mercado, E.; Larrosa-Haro, A.; Comas-Basté, O.; Latorre-Moratalla, M. L.; Veciana-Nogués, M. T.; Vidal-Carou, M. C. Influence of the Type of Breastfeeding and Human Milk Polyamines on Infant Anthropometric Parameters. *Frontiers in Nutrition* **2022**, *8*, 815477.
(42) Hernández-Jover, T.; Izquierdo-Pulido, M.; Veciana-Nogués, M. T.; Mariné-Font, A.; Vidal-Carou, M. C. Biogenic amine and polyamine contents in meat and meat products. *J. Agric. Food Chem.* **1997**, *45* (6), 2098−2102.
(43) Smela, D.; Pechova, P.; Komprda, T.; Klejdus, B.; Kuban, V. Liquid chromatographic determination of biogenic amines in a meat product during fermentation and long-term storage. *Czech journal of food sciences* **2003**, *21* (5), 167−175.
(44) Ruiz-Capillas, C.; Jiménez-Colmenero, F. Biogenic amine content in Spanish retail market meat products treated with protective atmosphere and high pressure. *European Food Research and Technology* **2004**, *218*, 237−241.
(45) Abbasi-Moayed, S.; Bigdeli, A.; Hormozi-Nezhad, M. R. Determination of spermine and spermidine in meat with a ratiometric fluorescence nanoprobe and a combinational logic gate. *Food Chem.* **2022**, *384*, 132459.
(46) Kozová, M.; Kalač, P.; Pelikánová, T. Contents of biologically active polyamines in chicken meat, liver, heart and skin after slaughter and their changes during meat storage and cooking. *Food chemistry* **2009**, *116* (2), 419−425.
(47) Zhao, A.; Sun, W. In *in silico Automatic Annotation of Phenolamides in Plants by Tandem Mass Spectra*; 2021 IEEE International Conference on Health, Instrumentation & Measurement, and Natural Sciences (InHeNce); IEEE: 2021; pp 1−5.
(48) Wang, S.; Suh, J. H.; Hung, W.-L.; Zheng, X.; Wang, Y.; Ho, C.-T. Use of UHPLC-TripleQ with synthetic standards to profile anti-inflammatory hydroxycinnamic acid amides in root barks and leaves of Lycium barbarum. *journal of food and drug analysis* **2018**, *26* (2), 572−582.
(49) Liu, X.; Osawa, T. Cis astaxanthin and especially 9-cis astaxanthin exhibits a higher antioxidant activity in vitro compared to the all-trans isomer. *Biochemical and biophysical research communications* **2007**, *357* (1), 187−193.
(50) Lal, N.; Berenjian, A. Cis and trans isomers of the vitamin menaquinone-7: which one is biologically significant? *Applied microbiology and biotechnology* **2020**, *104*, 2765−2776.

(51) Li, W.-C.; Wang, X.-Y.; Lin, P.-C.; Hu, N.; Zhang, Q.-L.; Suo, Y.-R.; Ding, C.-X. Preparative separation and purification of four cis-trans isomers of coumaroylspermidine analogs from safflower by high-speed counter-current chromatography. *Journal of Chromatography B* **2013**, *938*, 75−79.
(52) Kim, S. B.; Liu, Q.; Ahn, J. H.; Jo, Y. H.; Turk, A.; Hong, I. P.; Han, S. M.; Hwang, B. Y.; Lee, M. K. Polyamine derivatives from the bee pollen of Quercus mongolica with tyrosinase inhibitory activity. *Bioorganic Chemistry* **2018**, *81*, 127−133.
(53) Putschögl, M.; Zirak, P.; Penzkofer, A. Absorption and emission behaviour of trans-p-coumaric acid in aqueous solutions and some organic solvents. *Chem. Phys.* **2008**, *343* (1), 107−120.
(54) Xiang, J.; Zhang, M.; Apea-Bah, F. B.; Beta, T. Hydroxycinnamic acid amide (HCAA) derivatives, flavonoid C-glycosides, phenolic acids and antioxidant properties of foxtail millet. *Food chemistry* **2019**, *295*, 214−223.
(55) Zhou, Z.-Q.; Fan, H.-X.; He, R.-R.; Xiao, J.; Tsoi, B.; Lan, K.-H.; Kurihara, H.; So, K.-F.; Yao, X.-S.; Gao, H. Lycibarbarspermidines A-O, new dicaffeoylspermidine derivatives from wolfberry, with activities against Alzheimer's disease and oxidation. *Journal of agricultural and food chemistry* **2016**, *64* (11), 2223−2237.
(56) Leonard, W.; Zhang, P.; Ying, D.; Fang, Z. Tyramine-derived hydroxycinnamic acid amides in plant foods: sources, synthesis, health effects and potential applications in food industry. *Critical Reviews in Food Science and Nutrition* **2022**, *62* (6), 1608−1625.
(57) Becker, D.; Stegmüller, S.; Richling, E. Characterization of brewer's spent grain extracts by tandem mass spectrometry and HPLC-DAD: Ferulic acid dehydrodimers, phenolamides, and oxylipins. *Food Science & Nutrition* **2023**, *11* (5), 2298−2320.
(58) Qin, X.; Yin, Y.; Zhao, J.; An, W.; Fan, Y.; Liang, X.; Cao, Y. Metabolomic and transcriptomic analysis of Lycium chinese and L. ruthenicum under salinity stress. *BMC plant biology* **2022**, *22* (1), 8.
(59) Zhang, D.; Liu, J.; Zhang, Y.; Wang, H.; Wei, S.; Zhang, X.; Zhang, D.; Ma, H.; Ding, Q.; Ma, L. Morphophysiological, proteomic and metabolomic analyses reveal cadmium tolerance mechanism in common wheat (Triticum aestivum L.). *Journal of Hazardous Materials* **2023**, *445*, 130499.
(60) Narváez-Cuenca, C.-E.; Vincken, J.-P.; Zheng, C.; Gruppen, H. Diversity of (dihydro) hydroxycinnamic acid conjugates in Colombian potato tubers. *Food chemistry* **2013**, *139* (1−4), 1087−1097.
(61) Wang, S.; Suh, J. H.; Zheng, X.; Wang, Y.; Ho, C.-T. Identification and quantification of potential anti-inflammatory hydroxycinnamic acid amides from wolfberry. *Journal of agricultural and food chemistry* **2017**, *65* (2), 364−372.
(62) Assefa, S. T.; Yang, E.-Y.; Asamenew, G.; Kim, H.-W.; Cho, M.-C.; Lee, J. Identification of α-glucosidase inhibitors from leaf extract of pepper (Capsicum spp.) through metabolomic analysis. *Metabolites* **2021**, *11* (10), 649.
(63) Bento-Silva, A.; Duarte, N.; Belo, M.; Mecha, E.; Carbas, B.; Brites, C.; Vaz Patto, M. C.; Bronze, M. R. Shedding Light on the Volatile Composition of Broa, a Traditional Portuguese Maize Bread. *Biomolecules* **2021**, *11* (10), 1396.
(64) Jiang, Y.; Fang, Z.; Leonard, W.; Zhang, P. Phenolic compounds in Lycium berry: Composition, health benefits and industrial applications. *Journal of Functional Foods* **2021**, *77*, 104340.
(65) Tsivelika, N.; Irakli, M.; Mavromatis, A.; Chatzopoulou, P.; Karioti, A. Phenolic profile by HPLC-PDA-MS of Greek chamomile populations and commercial varieties and their antioxidant activity. *Foods* **2021**, *10* (10), 2345.
(66) Hegazi, N. M.; Khattab, A. R.; Frolov, A.; Wessjohann, L. A.; Farag, M. A. Authentication of saffron spice accessions from its common substitutes via a multiplex approach of UV/VIS fingerprints and UPLC/MS using molecular networking and chemometrics. *Food chemistry* **2022**, *367*, 130739.
(67) Li, Q.-W.; Zhang, R.; Zhou, Z.-Q.; Sun, W.-Y.; Fan, H.-X.; Wang, Y.; Xiao, J.; So, K.-F.; Yao, X.-S.; Gao, H. Phenylpropanoid glycosides from the fruit of Lycium barbarum L. and their bioactivity. *Phytochemistry* **2019**, *164*, 60−66.
(68) Caldas, F. R.; Augusto, F.; Facundo, H. T.; Alves, R. F.; dos Santos, F. d. A.; Silva, G. R. d.; Camara, C. A.; Silva, T. Chemical composition, antiradicalar and antimicrobial activity of Fabaceae pollen bee. *Química Nova* **2019**, *42*, 49−56.
(69) Wu, W.; Qiao, J.; Xiao, X.; Kong, L.; Dong, J.; Zhang, H. In vitro and In vivo digestion comparison of bee pollen with or without wall-disruption. *Journal of the Science of Food and Agriculture* **2021**, *101* (7), 2744−2755.
(70) Zhang, H.; Lu, Q.; Liu, R. Widely targeted metabolomics analysis reveals the effect of fermentation on the chemical composition of bee pollen. *Food Chem.* **2022**, *375*, 131908.
(71) Pihlava, J.-M. Identification of hordatines and other phenolamides in barley (Hordeum vulgare) and beer by UPLC-QTOF-MS. *Journal of cereal science* **2014**, *60* (3), 645−652.
(72) Dong, X.; Gao, Y.; Chen, W.; Wang, W.; Gong, L.; Liu, X.; Luo, J. Spatiotemporal distribution of phenolamides and the genetics of natural variation of hydroxycinnamoyl spermidine in rice. *Molecular Plant* **2015**, *8* (1), 111−121.
(73) Kyselka, J.; Bleha, R.; Dragoun, M.; Bialasová, K. n.; Horáčková, S. a. r.; Schätz, M.; Sluková, M.; Filip, V.; Synytsya, A. Antifungal polyamides of hydroxycinnamic acids from sunflower bee pollen. *Journal of agricultural and food chemistry* **2018**, *66* (42), 11018−11026.
(74) Pihlava, J.-M.; Hellström, J.; Kurtelius, T.; Mattila, P. Flavonoids, anthocyanins, phenolamides, benzoxazinoids, lignans and alkylresorcinols in rye (Secale cereale) and some rye products. *Journal of Cereal Science* **2018**, *79*, 183−192.
(75) Tiozon, R. J. N.; Sartagoda, K. J. D.; Serrano, L. M. N.; Fernie, A. R.; Sreenivasulu, N. Metabolomics based inferences to unravel phenolic compound diversity in cereals and its implications for human gut health. *Trends in Food Science Technology* **2022**, *127*, 14−25.
(76) Burt, A. J.; Arnason, J. T.; García-Lara, S. Natural variation of hydroxycinnamic acid amides in maize landraces. *Journal of cereal science* **2019**, *88*, 145−149.
(77) Ma, R.-H.; Zhang, X.-X.; Ni, Z.-J.; Thakur, K.; Wang, W.; Yan, Y.-M.; Cao, Y.-L.; Zhang, J.-G.; Rengasamy, K. R.; Wei, Z.-J. Lycium barbarum (Goji) as functional food: a review of its nutrition, phytochemical structure, biological features, and food industry prospects. *Critical Reviews in Food Science and Nutrition* **2023**, *63*, 10621.
(78) Shakya, R.; Navarre, D. A. Rapid screening of ascorbic acid, glycoalkaloids, and phenolics in potato using high-performance liquid chromatography. *Journal of Agricultural and food Chemistry* **2006**, *54* (15), 5253−5260.
(79) Chong, E. S. L.; McGhie, T. K.; Heyes, J. A.; Stowell, K. M. Metabolite profiling and quantification of phytochemicals in potato extracts using ultra-high-performance liquid chromatography-mass spectrometry. *Journal of the Science of Food and Agriculture* **2013**, *93* (15), 3801−3808.
(80) Pegg, A. E. Functions of polyamines in mammals. *J. Biol. Chem.* **2016**, *291* (29), 14904−14912.
(81) Lenis, Y. Y.; Elmetwally, M. A.; Maldonado-Estrada, J. G.; Bazer, F. W. Physiological importance of polyamines. *Zygote* **2017**, *25* (3), 244−255.
(82) Uemura, T.; Akasaka, Y.; Ikegaya, H. Correlation of polyamines, acrolein-conjugated lysine and polyamine metabolic enzyme levels with age in human liver. *Heliyon* **2020**, *6* (9), e05031.
(83) Eisenberg, T.; Knauer, H.; Schauer, A.; Buttner, S.; Ruckenstuhl, C.; Carmona-Gutierrez, D.; Ring, J.; Schroeder, S.; Magnes, C.; Antonacci, L.; Fussi, H.; Deszcz, L.; Hartl, R.; Schraml, E.; Criollo, A.; Megalou, E.; Weiskopf, D.; Laun, P.; Heeren, G.; Breitenbach, M.; Grubeck-Loebenstein, B.; Herker, E.; Fahrenkrog, B.; Frohlich, K.-U.; Sinner, F.; Tavernarakis, N.; Minois, N.; Kroemer, G.; Madeo, F. Induction of autophagy by spermidine promotes longevity. *Nature cell biology* **2009**, *11* (11), 1305−1314.
(84) Eisenberg, T.; Abdellatif, M.; Schroeder, S.; Primessnig, U.; Stekovic, S.; Pendl, T.; Harger, A.; Schipke, J.; Zimmermann, A.; Schmidt, A.; Tong, M.; Ruckenstuhl, C.; Dammbrueck, C.; Gross, A. S; Herbst, V.; Magnes, C.; Trausinger, G.; Narath, S.; Meinitzer, A.;

https://doi.org/10.1021/acs.jafc.3c08556
J. Agric. Food Chem. 2024, 72, 5089−5106

Hu, Z.; Kirsch, A.; Eller, K.; Carmona-Gutierrez, D.; Buttner, S.; Pietrocola, F.; Knittelfelder, O.; Schrepfer, E.; Rockenfeller, P.; Simonini, C.; Rahn, A.; Horsch, M.; Moreth, K.; Beckers, J.; Fuchs, H.; Gailus-Durner, V.; Neff, F.; Janik, D.; Rathkolb, B.; Rozman, J.; de Angelis, M. H.; Moustafa, T.; Haemmerle, G.; Mayr, M.; Willeit, P.; von Frieling-Salewsky, M.; Pieske, B.; Scorrano, L.; Pieber, T.; Pechlaner, R.; Willeit, J.; Sigrist, S. J; Linke, W. A; Muhlfeld, C.; Sadoshima, J.; Dengjel, J.; Kiechl, S.; Kroemer, G.; Sedej, S.; Madeo, F. Cardioprotection and lifespan extension by the natural polyamine spermidine. *Nature medicine* **2016**, *22* (12), 1428−1438.

(85) Madeo, F.; Eisenberg, T.; Büttner, S.; Ruckenstuhl, C.; Kroemer, G. Spermidine: a novel autophagy inducer and longevity elixir. *Autophagy* **2010**, *6* (1), 160−162.

(86) Madeo, F.; Eisenberg, T.; Pietrocola, F.; Kroemer, G. Spermidine in health and disease. *Science* **2018**, *359* (6374), No. eaan2788.

(87) Soda, K.; Dobashi, Y.; Kano, Y.; Tsujinaka, S.; Konishi, F. Polyamine-rich food decreases age-associated pathology and mortality in aged mice. *Experimental gerontology* **2009**, *44* (11), 727−732.

(88) Matsumoto, M.; Kitada, Y.; Naito, Y. Endothelial function is improved by inducing microbial polyamine production in the gut: a randomized placebo-controlled trial. *Nutrients* **2019**, *11* (5), 1188.

(89) Kiechl, S.; Pechlaner, R.; Willeit, P.; Notdurfter, M.; Paulweber, B.; Willeit, K.; Werner, P.; Ruckenstuhl, C.; Iglseder, B.; Weger, S. Higher spermidine intake is linked to lower mortality: a prospective population-based study. *American journal of clinical nutrition* **2018**, *108* (2), 371−380.

(90) Pekar, T.; Wendzel, A.; Flak, W.; Kremer, A.; Pauschenwein-Frantsich, S.; Gschaider, A.; Wantke, F.; Jarisch, R. Spermidine in dementia: Relation to age and memory performance. *Wiener klinische Wochenschrift* **2020**, *132* (1−2), 42−46.

(91) Zhang, H.; Wang, J.; Li, L.; Chai, N.; Chen, Y.; Wu, F.; Zhang, W.; Wang, L.; Shi, S.; Zhang, L.; Bian, S.; Xu, C.; Tian, Y.; Zhao, Y. Spermine and spermidine reversed age-related cardiac deterioration in rats. *Oncotarget* **2017**, *8* (39), 64793.

(92) Soda, K. Polyamine intake, dietary pattern, and cardiovascular disease. *Medical hypotheses* **2010**, *75* (3), 299−301.

(93) Soda, K.; Kano, Y.; Chiba, F. Food polyamine and cardiovascular disease-an epidemiological study. *Global journal of health science* **2012**, *4* (6), 170.

(94) Nowotarski, S. L.; Woster, P. M.; Casero, R. A. Polyamines and cancer: implications for chemotherapy and chemoprevention. *Expert reviews in molecular medicine* **2013**, *15*, No. e3.

(95) Gerner, E. W.; Bruckheimer, E.; Cohen, A. Cancer pharmacoprevention: Targeting polyamine metabolism to manage risk factors for colon cancer. *J. Biol. Chem.* **2018**, *293* (48), 18770−18778.

(96) Wirth, M.; Schwarz, C.; Benson, G.; Horn, N.; Buchert, R.; Lange, C.; Kobe, T.; Hetzer, S.; Maglione, M.; Michael, E.; Marschenz, S.; Mai, K.; Kopp, U.; Schmitz, D.; Grittner, U.; Sigrist, S. J.; Stekovic, S.; Madeo, F.; Floel, A. Effects of spermidine supplementation on cognition and biomarkers in older adults with subjective cognitive decline (SmartAge)—study protocol for a randomized controlled trial. *Alzheimer's research therapy* **2019**, *11*, 36.

(97) Soda, K.; Kano, Y.; Chiba, F.; Koizumi, K.; Miyaki, Y. Increased polyamine intake inhibits age-associated alteration in global DNA methylation and 1, 2-dimethylhydrazine-induced tumorigenesis. *PLoS One* **2013**, *8* (5), No. e64357.

(98) Pietrocola, F.; Pol, J.; Vacchelli, E.; Rao, S.; Enot, D. P.; Baracco, E. E.; Levesque, S.; Castoldi, F.; Jacquelot, N.; Yamazaki, T.; Senovilla, L.; Marino, G.; Aranda, F.; Durand, S.; Sica, V.; Chery, A.; Lachkar, S.; Sigl, V.; Bloy, N.; Buque, A.; Falzoni, S.; Ryffel, B.; Apetoh, L.; Di Virgilio, F.; Madeo, F.; Maiuri, M. C.; Zitvogel, L.; Levine, B.; Penninger, J. M.; Kroemer, G. Caloric restriction mimetics enhance anticancer immunosurveillance. *Cancer cell* **2016**, *30* (1), 147−160.

(99) Yue, F.; Li, W.; Zou, J.; Jiang, X.; Xu, G.; Huang, H.; Liu, L. Spermidine prolongs lifespan and prevents liver fibrosis and hepatocellular carcinoma by activating MAP1S-mediated autophagy. *Cancer research* **2017**, *77* (11), 2938−2951.

(100) Di Biase, S.; Lee, C.; Brandhorst, S.; Manes, B.; Buono, R.; Cheng, C.-W.; Cacciottolo, M.; Martin-Montalvo, A.; de Cabo, R.; Wei, M.; Morgan, T. E.; Longo, V. D. Fasting-mimicking diet reduces HO-1 to promote T cell-mediated tumor cytotoxicity. *Cancer cell* **2016**, *30* (1), 136−146.

(101) Matsumoto, M.; Kibe, R.; Ooga, T.; Aiba, Y.; Kurihara, S.; Sawaki, E.; Koga, Y.; Benno, Y. Impact of intestinal microbiota on intestinal luminal metabolome. *Sci. Rep.* **2012**, *2* (1), 233.

(102) Zhong, Z.; Sanchez-Lopez, E.; Karin, M. Autophagy, NLRP3 inflammasome and auto-inflammatory/immune diseases. *Clinical and experimental rheumatology* **2016**, *34* (4 Suppl 98), 12−16.

(103) Kibe, R.; Kurihara, S.; Sakai, Y.; Suzuki, H.; Ooga, T.; Sawaki, E.; Muramatsu, K.; Nakamura, A.; Yamashita, A.; Kitada, Y.; Kakeyama, M.; Benno, Y.; Matsumoto, M. Upregulation of colonic luminal polyamines produced by intestinal microbiota delays senescence in mice. *Sci. Rep.* **2014**, *4* (1), 4548.

(104) Zhu, S.; Ashok, M.; Li, J.; Li, W.; Yang, H.; Wang, P.; Tracey, K. J.; Sama, A. E.; Wang, H. Spermine protects mice against lethal sepsis partly by attenuating surrogate inflammatory markers. *Mol. Med.* **2009**, *15* (7), 275−282.

(105) Soda, K.; Uemura, T.; Sanayama, H.; Igarashi, K.; Fukui, T. Polyamine-rich diet elevates blood spermine levels and inhibits pro-inflammatory status: an interventional study. *Medical Sciences* **2021**, *9* (2), 22.

(106) Yang, Q; Zheng, C; Cao, J; Cao, G; Shou, P; Lin, L; Velletri, T; Jiang, M; Chen, Q; Han, Y; Li, F; Wang, Y; Cao, W; Shi, Y Spermidine alleviates experimental autoimmune encephalomyelitis through inducing inhibitory macrophages. *Cell Death Differentiation* **2016**, *23* (11), 1850−1861.

(107) Choi, Y. H.; Park, H. Y. Anti-inflammatory effects of spermidine in lipopolysaccharide-stimulated BV2 microglial cells. *Journal of biomedical science* **2012**, *19* (1), 31.

(108) Gao, Y.; Wu, A.; Li, Y.; Chang, Y.; Xue, C.; Tang, Q. The risk of carrageenan-induced colitis is exacerbated under high-sucrose/high-salt diet. *Int. J. Biol. Macromol.* **2022**, *210*, 475−482.

(109) Sadasivan, S. K.; Vasamsetti, B.; Singh, J.; Marikunte, V. V.; Oommen, A. M.; Jagannath, M.R.; Pralhada Rao, R. Exogenous administration of spermine improves glucose utilization and decreases bodyweight in mice. *European journal of pharmacology* **2014**, *729*, 94−99.

(110) Ramos-Molina, B.; Queipo-Ortuño, M. I.; Lambertos, A.; Tinahones, F. J.; Peñafiel, R. Dietary and gut microbiota polyamines in obesity-and age-related diseases. *Frontiers in Nutrition* **2019**, *6*, 24.

(111) Akasaka, N.; Fujiwara, S. The therapeutic and nutraceutical potential of agmatine, and its enhanced production using Aspergillus oryzae. *Amino Acids* **2020**, *52* (2), 181−197.

(112) Fernandez, A. F; Barcena, C.; Martinez-Garcia, G. G; Tamargo-Gomez, I.; Suarez, M. F; Pietrocola, F.; Castoldi, F.; Esteban, L.; Sierra-Filardi, E.; Boya, P.; Lopez-Otin, C.; Kroemer, G.; Marino, G. Autophagy couteracts weight gain, lipotoxicity and pancreatic β-cell death upon hypercaloric pro-diabetic regimens. *Cell death & disease* **2017**, *8* (8), No. e2970.

(113) Gugliucci, A.; Menini, T. The polyamines spermine and spermidine protect proteins from structural and functional damage by AGE precursors: a new role for old molecules? *Life sciences* **2003**, *72* (23), 2603−2616.

(114) Wu, X.; Cao, W.; Jia, G.; Zhao, H.; Chen, X.; Wu, C.; Tang, J.; Wang, J.; Liu, G. New insights into the role of spermine in enhancing the antioxidant capacity of rat spleen and liver under oxidative stress. *Animal Nutrition* **2017**, *3* (1), 85−90.

(115) Ha, H. C.; Sirisoma, N. S.; Kuppusamy, P.; Zweier, J. L.; Woster, P. M.; Casero, R. A., Jr The natural polyamine spermine functions directly as a free radical scavenger. *Proc. Natl. Acad. Sci. U. S. A.* **1998**, *95* (19), 11140−11145.

(116) Chai, N.; Zhang, H.; Li, L.; Yu, X.; Liu, Y.; Lin, Y.; Wang, L.; Yan, J.; Nikolaevna, S. E.; Zhao, Y. Spermidine prevents heart injury in neonatal rats exposed to intrauterine hypoxia by inhibiting

https://doi.org/10.1021/acs.jafc.3c08556
J. Agric. Food Chem. 2024, 72, 5089−5106

oxidative stress and mitochondrial fragmentation. *Oxidative medicine and cellular longevity* **2019**, *2019*, 1.
(117) Clarkson, A. N.; Liu, H.; Pearson, L.; Kapoor, M.; Harrison, J. C.; Sammut, I. A.; Jackson, D. M.; Appleton, I. Neuroprotective effects of spermine following hypoxia-ischemia-induced brain damage: a mechanistic study. *FASEB J.* **2004**, *18* (10), 1114−1116.
(118) Jeong, J.-W.; Cha, H.-J.; Han, M. H.; Hwang, S. J.; Lee, D.-S.; Yoo, J. S.; Choi, I.-W.; Kim, S.; Kim, H.-S.; Kim, G.-Y.; Hong, S. H.; Park, C.; Lee, H.-J.; Choi, Y. H. Spermidine protects against oxidative stress in inflammation models using macrophages and zebrafish. *Biomolecules therapeutics* **2018**, *26* (2), 146.
(119) Akhova, A. V.; Tkachenko, A. G. Multifaceted role of polyamines in bacterial adaptation to antibiotic-mediated oxidative stress. *Microbiological Society of Korea* **2020**, *56* (2), 103−110.
(120) Toro-Funes, N.; Bosch-Fusté, J.; Veciana-Nogués, M. T.; Izquierdo-Pulido, M.; Vidal-Carou, M. C. In vitro antioxidant activity of dietary polyamines. *Food research international* **2013**, *51* (1), 141−147.
(121) Makletsova, M. G.; Syatkin, S. P.; Poleshchuk, V. V.; Urazgildeeva, G. R.; Chigaleychik, L. A.; Sungrapova, C. Y.; Illarioshkin, S. N. Polyamines in Parkinson's disease: their role in oxidative stress induction and protein aggregation. *Journal of Neurology Research* **2019**, *9* (1−2), 1−7.
(122) Minois, N.; Rockenfeller, P.; Smith, T. K.; Carmona-Gutierrez, D. Spermidine feeding decreases age-related locomotor activity loss and induces changes in lipid composition. *PloS one* **2014**, *9* (7), No. e102435.
(123) Noro, T.; Namekata, K.; Kimura, A.; Guo, X.; Azuchi, Y.; Harada, C.; Nakano, T.; Tsuneoka, H.; Harada, T. Spermidine promotes retinal ganglion cell survival and optic nerve regeneration in adult mice following optic nerve injury. *Cell death disease* **2015**, *6* (4), No. e1720.
(124) Noro, T.; Namekata, K.; Azuchi, Y.; Kimura, A.; Guo, X.; Harada, C.; Nakano, T.; Tsuneoka, H.; Harada, T. Spermidine ameliorates neurodegeneration in a mouse model of normal tension glaucoma. *Investigative ophthalmology & visual science* **2015**, *56* (8), 5012−5019.
(125) Neis, V. B.; Rosa, P. B.; Olescowicz, G.; Rodrigues, A. L. S. Therapeutic potential of agmatine for CNS disorders. *Neurochemistry international* **2017**, *108*, 318−331.
(126) Valverde, A. P.; Camargo, A.; Rodrigues, A. L. S. Agmatine as a novel candidate for rapid-onset antidepressant response. *World Journal of Psychiatry* **2021**, *11* (11), 981.
(127) Barua, S.; Kim, J. Y.; Kim, J. Y.; Kim, J. H.; Lee, J. E. Therapeutic effect of agmatine on neurological disease: focus on ion channels and receptors. *Neurochemical research* **2019**, *44*, 735−750.
(128) Leander, G. A preliminary investigation on the therapeutic effect of Cernilton N in chronic prostatovesiculitis. *Svenska Lakartidningen* **1962**, *59* (45), 3296.
(129) Jethon, Z.; Kielan-Bak, Z.; Tara, B.; Ziolkowska, B. Effect of Cernilton on Anaerobic Metabolism. Graminex.
(130) Zhang, H.; Zhu, X.; Huang, Q.; Zhang, L.; Liu, X.; Liu, R.; Lu, Q. Antioxidant and anti-inflammatory activities of rape bee pollen after fermentation and their correlation with chemical components by ultra-performance liquid chromatography-quadrupole time of flight mass spectrometry-based untargeted metabolomics. *Food Chem.* **2023**, *409*, 135342.
(131) Liu, X.; Zheng, X.; Long, Y.; Cao, H.; Wang, N.; Lu, Y.; Zhao, K.; Zhou, H.; Zheng, J. Dual targets guided screening and isolation of Kukoamine B as a novel natural anti-sepsis agent from traditional Chinese herb Cortex lycii. *International immunopharmacology* **2011**, *11* (1), 110−120.
(132) Liu, X.; Zheng, X.; Wang, N.; Cao, H.; Lu, Y.; Long, Y.; Zhao, K.; Zhou, H.; Zheng, J. Kukoamine B, a novel dual inhibitor of LPS and CpG DNA, is a potential candidate for sepsis treatment. *British journal of pharmacology* **2011**, *162* (6), 1274−1290.
(133) Yang, D.; Zheng, X.; Wang, N.; Fan, S.; Yang, Y.; Lu, Y.; Chen, Q.; Liu, X.; Zheng, J. Kukoamine B promotes TLR4-independent lipopolysaccharide uptake in murine hepatocytes. *Oncotarget* **2016**, *7* (36), 57498.
(134) Li, Y.-Y.; Stewart, D. A.; Ye, X.-M.; Yin, L.-H.; Pathmasiri, W. W.; McRitchie, S. L.; Fennell, T. R.; Cheung, H.-Y.; Sumner, S. J. A metabolomics approach to investigate kukoamine B—A potent natural product with anti-diabetic properties. *Frontiers in pharmacology* **2019**, *9*, 1575.
(135) Jiang, G.; Takase, M.; Aihara, Y.; Shigemori, H. Inhibitory activities of kukoamines A and B from Lycii Cortex on amyloid aggregation related to Alzheimer's disease and type 2 diabetes. *Journal of natural medicines* **2020**, *74*, 247−251.
(136) Li, G.; Zhou, F.; Chen, Y.; Zhang, W.; Wang, N. Kukoamine A attenuates insulin resistance and fatty liver through downregulation of Srebp-1c. *Biomedicine & Pharmacotherapy* **2017**, *89*, 536−543.
(137) Khongkarat, P.; Ramadhan, R.; Phuwapraisirisan, P.; Chanchao, C. Safflospermidines from the bee pollen of Helianthus annuus L. exhibit a higher in vitro antityrosinase activity than kojic acid. *Heliyon* **2020**, *6* (3), e03638.
(138) Choi, S. W.; Lee, S. K.; Kim, E. O.; Oh, J. H.; Yoon, K. S.; Parris, N.; Hicks, K. B.; Moreau, R. A. Antioxidant and antimelanogenic activities of polyamine conjugates from corn bran and related hydroxycinnamic acids. *J. Agric. Food Chem.* **2007**, *55* (10), 3920−3925.
(139) Hu, X.-L.; Gao, L.-Y.; Niu, Y.-X.; Tian, X.; Wang, J.; Meng, W.-H.; Zhang, Q.; Cui, C.; Han, L.; Zhao, Q.-C. Neuroprotection by Kukoamine A against oxidative stress may involve N-methyl-D-aspartate receptors. *Biochimica et Biophysica Acta (BBA)-General Subjects* **2015**, *1850* (2), 287−298.
(140) Hu, X.; Song, Q.; Li, X.; Li, D.; Zhang, Q.; Meng, W.; Zhao, Q. Neuroprotective effects of Kukoamine A on neurotoxin-induced Parkinson's model through apoptosis inhibition and autophagy enhancement. *Neuropharmacology* **2017**, *117*, 352−363.
(141) Liu, J.; Jiang, X.; Zhang, Q.; Lin, S.; Zhu, J.; Zhang, Y.; Du, J.; Hu, X.; Meng, W.; Zhao, Q. Neuroprotective effects of Kukoamine A against cerebral ischemia via antioxidant and inactivation of apoptosis pathway. *Neurochemistry international* **2017**, *107*, 191−197.
(142) Zhang, Y.; Cheng, Z.; Wang, C.; Ma, H.; Meng, W.; Zhao, Q. Neuroprotective effects of kukoamine a against radiation-induced rat brain injury through inhibition of oxidative stress and neuronal apoptosis. *Neurochem. Res.* **2016**, *41*, 2549−2558.
(143) Zhang, Y.; Gao, L.; Cheng, Z.; Cai, J.; Niu, Y.; Meng, W.; Zhao, Q. Kukoamine A prevents radiation-induced neuroinflammation and preserves hippocampal neurogenesis in rats by inhibiting activation of NF-κB and AP-1. *Neurotoxicity research* **2017**, *31*, 259−268.
(144) Wang, Q.; Li, H.; Sun, Z.; Dong, L.; Gao, L.; Liu, C.; Wang, X. Kukoamine A inhibits human glioblastoma cell growth and migration through apoptosis induction and epithelial-mesenchymal transition attenuation. *Sci. Rep.* **2016**, *6* (1), 36543.
(145) Ma, C.-M.; Nakamura, N.; Hattori, M. Inhibitory effects on HIV-1 protease of tri-p-coumaroylspermidine from Artemisia caruifolia and related amides. *Chemical and pharmaceutical bulletin* **2001**, *49* (7), 915−917.
(146) Mude, H.; Balapure, A.; Thakur, A.; Ganesan, R.; Ray Dutta, J. Enhanced antibacterial, antioxidant and anticancer activity of caffeic acid by simple acid-base complexation with spermine/spermidine. *Natural Product Research* **2022**, *36* (24), 6453−6458.
(147) Zhang, H.; Liu, R.; Lu, Q. Separation and characterization of phenolamines and flavonoids from rape bee pollen, and comparison of their antioxidant activities and protective effects against oxidative stress. *Molecules* **2020**, *25* (6), 1264.

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