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Article

Biogenic Amines from Herbal and Waste Sources: Neuroprotective and Therapeutic Implications

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Abstract: The current manuscript provides a comprehensive review of biogenic amines (BAs), with a special focus on those derived from herbal sources such as banana peels and their therapeutic potential in central nervous system (CNS) disorders. Biogenic amines, including dopamine, serotonin, epinephrine, and polyamines, are biologically active compounds that play significant roles in neurotransmission, physiological regulation, and plant defense. The review highlights plant sources rich in these compounds, particularly banana species, and discusses innovative extraction and identification methods, such as solid-phase extraction (SPE), HPLC, and GC-MS. Emphasis is placed on the valorization of agricultural waste as a sustainable source of neuroactive compounds, which supports a circular bioeconomy. Potential applications in treating neurodegenerative diseases such as Parkinson's and depression are discussed, along with the toxicological considerations of excessive BA accumulation. This review aims to provide insight into the isolation, application, and future potential of BAs from herbal and waste materials for therapeutic and ecological benefits.

Keywords: biogenic amines; banana peel; herbal neurotherapy; dopamine; serotonin; circular bioeconomy

Introduction

Biogenic Amines: As Cell-Protective Mediators

The Biogenic amines acting as neuro-transmittors such as dopamine, Nor-epinephrine, epinephrine and serotonin have much major implication in neuronal regulation of nervous system. The functions of these chemical messengers are varied among living species including plants[1, 2], animals[3] and micro-organisms[4]. In animals, these biogenic amines have selective roles exerting as neuto-protective, as well as neuro-toxic effects[3]. Biogenic amines in particular, polyamines have played the protective role in many micro-organisms[4] against reactive oxygen species produced during the defense against the host system. This intern precludes the major area of research including their finding of detailed molecular mechanisms and based on their chemical and biological properties, the selective isolation of these biogenic amines would contribute the effective therapy for various neuronal diseases.

Physical and Chemical Properties of Biogenic Amines

Thermodynamic properties of Biogenic Amines have been thoroughly investigated, including vapour pressure measurements, solid-liquid equilibria, and many other significant components for physical assessment.[5] Biogenic amines are organic nitrogen molecules with low molecular weights. Their chemical structure can be classified as (i) aromatic and heterocyclic (histamine, tryptamine, tyramine, phenylethylamine, and serotonin); (ii) aliphatic di-, tri-, and polyamines (putrescine, cadaverine, spermine, spermidine, and agmatine); and (iii) aliphatic volatile amines (ethylamine, methylamine, isopentylamine, and ethanolamine). Furthermore, their amine group classifications include (i) monoamine (phenylethylamine, tyramine, methylamine, ethylamine, isopentylamine, and ethanolamine), (ii) diamine (histamine, tryptamine, seratonin, putrescine, and cadaverine), and (iii)

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polyamine (spermine, spermidine, and agmatine). Biogenic amines have varying log P, pKa, and water solubility.[6] As a result; they exhibit basic, acidic, and amphoteric characteristics.[6]

Biogenic Amine Based Identification, Detection and Quantification

There are distinct methods available for Separation and identification of biogenic amines (Table 1). Besides that, for isolation of selective biogenic amine, an analyst has to consider log P, pKa and solubility properties for efficient isolation method to be developed. However, there are two ways to detect BAs, first; by detecting microorganisms that possess the ability to produce BAs, second; by directly quantifying BAs. The formation of BA can be verified by changes in mediumcolor and pH [36]. Most detection methods for BAs have been developed based on chromatographytechnology. HPLC with fluorescence detection, UV detection, or mass spectrometry detection after derivatization of benzoyl chloride [37], dansyl chloride [38], and o-phthalaldehyde [39] have was successfully used.

The high-performance liquid chromatography (HPLC) [40], gas chromatography (GC) [41], thin-layer chromatography (TLC) [42], ion exchange chromatography [43], biosensors [44], and capillary electrophoresis (CE) [45]are the method used for detection of BAs. It has been applied to wines [46], soybean paste [47], and pepperoni sausage [48]to determine BA levels. To provide a chromophore forUV or fluorescence detection, their polarity needs to be reduced. This process is generally done by derivatization [48]. Dansyl chloride [49], benzoyl chloride [50], and o-phthalaldehyde [51]are generallyused for derivatization. Extraction is one practical step used in most BA detection techniques.

Tang et al. [52]have reported the detection of BAs in sufu through HPLC with solid-phase extraction (SPE) and pre-column derivatization. HPLC with direct derivatization of acid extract has been used to quantify BAs in cheese [49]. To determine BAs in Port wine and grape juice, Fernandes and Ferreira [53] have employed gas chromatographic-mass spectrophotometric method in selected ion-monitoring mode using heptafluorobutyric anhydride as a derivatization reagent. Capillary electrophoresis with conductometric detection has been used to detect BAs in food without any derivatization steps [54].

Competitive direct-enzyme linked immunosorbent assay (CD-ELISA) is a non-complex and rapid method used to detect histamine in food products such as cheese [55]and wine [56]. Dadakova et al. [57] have demonstrated a rapid ultra-performance liquid chromatography (UPLC) to detect BAs. Ultra-high pressure liquid chromatography-electrospray tandem mass spectrometry(UHPLC-ESI-MS/MS) has been used to determine BAs in Cheonggukjang [58]. In addition, an enzyme sensor array has been proposed to simultaneously determine several types of BAs with less time required [59].

Table 1. Distinct chemical and biological properties of some major Biogenic amines in living organisms.

Type of Biogenic amine	Biological Source /occurrence	Log P	pKa	Suitable Seperation/extraction method used form biological source	Biological/Physiological Function	Toxicity in humans	Therapeutic Uses in Humans
Dopamine (Monoamine)	Animal : Brain Plant: Banana Species[1, 2]	−0.98 E[6]	9.27 10.01[6]	SPE, LLE[6]	Animal: Neurotransmitter Plant: Affect Photosynthesis	Dopamine toxicity involves mitochondrial complex I inhibition[3]	In Parkinsonism, Depression andother CNS disorders
Epinephrine (Monoamine)	Animal: Brain Plant: *Lemna paucicostata*[4], Banana Species[1, 2]	−1.37[6]	8.91 9.69[6]	HPLC[6]	Animal: Neurotransmitter Plant: cytoplasm movement, ion permeability, and membrane potential[4]	Long- lasting skinrashand dyspnea [7]	Anaphylaxis[7]
Nor-epinephrine (Monoamine)	Animal: brain Plant: *Lemna paucicostata* 6746 [4], Banana Species[1, 2]	−1.24 E −1.4[6]	8.85 9.5[6]	GC-MS[4]	Animal: Neurotransmitter Plant: Promote flowering under a photoperiodic regime of 8-h light	Uncontrolle d hypertensio n [8]	Treatment of cardiac arrest with profound hypotension [8]

					and 16-h darkness		
Tyramine (Monoamine)	Animal: In liver [6] Microorganisms: Cheese[9] (raw milk) containing *Enterococcus casseliflavus*, *Enterococcus durans*, *Enterococcus faecalis*, *Enterococcus faecium*, *Enterococcus hirae*, *Lactobacillus brevis*,	−2.26[6]	2 9.19[6]	LC-MS/MS[6]	Animal: Precursor for synthesis of dopamine, epinephrine andnor-epinephrine neurotransmitters Plant: Precursor of numerous specialized metabolites that have diverse physiological roles as electron carriers, antioxidants, attractants, and	*cheese effect*; which is characterized by hypertension, headache, and migraine[12]	Antioxidant, anti-inflammatory, anti-cancer, anti-diabetic, anti-melanogenesis and neuroprotective properties.[10]

	Lactobacillus curvatus, Streptococcus thermophilus. Plant: *Allium, Cannabis, Lycium, Polyganotum and Solanum*.[10], Banana Species[1, 2]				defense compounds.[11]		
Serotonin (Diamine)	Animal : Brain Plant: Banana Species[1,2]	0.21[6]	9.31 10^6	*On-line* micro dialysis technique[6]	Animal: Neurotransmitter Plant: Regulation of plant growth and stress response [13]	Serotonin syndrome [14]	Neuromodulator[14]
Histamine (Diamine)	Animal: fish, fermented sausages, fish sauce, dairy products[15] Plant: Banana Species[1, 2]	-0.70[16]	9.68 5.88[16]	Functionalized silica materials (cation-exchang e materials)[17]	Animal: Inflammatory mediator Plant: Biogenic amines in plantcell at normal and stress[18]	Histamine (Scombroid) Poisoning[12]	Regulating a range of physiological processes in vertebrates, including immunefunction and reproduction.[19]

Putrescine (Diamine)	Animal: fish, fermented sausages, fish sauce, dairy products [15] Plant: Wheat (*Triticum aesti vum* L.) Plants[20]	-0.70[16]	10.51 [16]	Functionalized silica materials (cation-exchang e materials)[17]	Animal: Putrescine Improves Growth Performance [21] Plant: Positive impact on plant growth and development.[22]	Potentiator s of toxic effect of other amines due to the inhibition of detoxifying enzymes.[12]	Essential to the angiogenesis process[23]
Cadaverine (Diamine)	Animal: Beef 24	-0.6 [26]	10.25 9.13 [26]	Functionalized silica materials	Animal: Cadaverine as a	Potentiator s of toxic	The potentiation of histamine's
	Plant: Barley seedlings [25]			(cation-exchang e materials)[17]	Potential Spoilage Indicator [24] Plant: Contributes to the health of plants by regulating plant growth and development, abiotic stress tolerance and antioxidant defense mechanisms.[25]	effect of other amines dueto the inhibition of detoxifying enzymes.[12]	toxic effect[27]

Spermine (Polyamine)	Animal: Mouse [28] Plant: *Arabidopsis*[29, 2]	-0.7 [30]	10.8 [30]	Functionalized silica materials (cation-exchang e materials)[17]	Animal: Decreases as prostate cancer progresses [28] Plant: effective in increasing plant resistance to biotic and abiotic stressors [31]	Toxicity of Acrolein Produced from Spermine[32]	Neuro-protective[3]
Spermidine (Polyamine)	Animal: Mouse [33] Plant: Common in allplants [2]	-1 [34]	10.53 [34]	Functionalized silica materials (cation-exchang e materials)[17]	Animal: Promoting the growth of ileal villi and jejunumvilli [33] Plant: callus induction, shoot multiplication, embryogenesis, organogenesis and rooting [2]	Excess of Spermidine simultaneo usly triggers the production of superoxide radicals [35]	Neuro-protective[3]

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Important Chemical Reactions and Biological Actions of Biogenic Amines

Chemical Reactions

Heat treatment of Biogenic amines[60]

Alkali heat treatment of soluble and insoluble proteins (lysozyme, phosvitin, α-casein, and keratin) with biogenic amines (phenylethylamine, histamine, putrescine, and spermine) produced new amino acids. The mechanism[61] was proposed to be the addition of amine to dehydroalanine, suggesting that the latter may originate, at least in some proteins, from serine residues. Prolonged heating, higher temperatures, higher pH, and increased amine concentration all improved the yield of the new amino acids.[61]. After Waalkes et al.'s discovery of noradrenaline in banana tissue, bananas as a potential source for hydroxylation enzymes and found that homogenates of different banana tissues were capable of converting hydroxytyramine to noradrenalin.[60]

Derivatization of Biogenic Amines[62]

The optimal conditions for the derivatization reaction of biogenic amines (histamine, tyramine, putrecine, tryptamine, phenylethylamine, cadaverine, spermidine, and spermine) with acetylacetone were found. In this reaction, the amount of K_2HPO_4, reaction time, reagent amount, solvent selection, and solvent amount were all optimized. As a consequence of this study, the best conditions were determined to be 2 g of K_2HPO_4, 20 minutes of reaction time, 1 mL of acetylacetone, methanol as the solvent, and 10 mL of solvent.

Biological Actions

Monoamines: Biosynthesis[63]

Biogenic amines (BA) (Table 1) are organic chemicals present in food, plants, and animals, as well as microbes that produce them. They are the result of a chemical process known as amino acid decarboxylation.

Monoamines: Physiological Significance[64]

First of all, BAs are substances that are necessary for the survival and functioning of cells in an organism's metabolic activity, including protein synthesis, hormone synthesis as well as DNA replication. On the other hand, despite their positive effects on the functioning of the organism, an excessive content of BAs proves to be toxic (diarrhea, food poisoning, vomiting, sweating or tachycardia). Biogenic amines are vasoactive components, and excessive doses cause changes in blood pressure in humans and animals. Examples of amines with important psychopharmacologic or vasodynamic effects are histamine, tryptamine, tyramine and phenylethylamine. Histamine is a biologically active substance that rapidly diffuses to tissues through blood circulation, which results in different effects.

Monoamines: Toxicity

Food poisoning due to consumption of fish containing high amounts of histamine causes dizziness, faintness, burning sensation in the mouth, inability to swallow, and itching [65]. Symptoms of poisoning can appear within several minutes to 3 h after ingestion of fish containing histamine at levels higher than 1 mg/g [66]. Tyramine, phenylethylamine, and tryptamine are mainly cause hypertension, headache, pupil dilatation, palpebral tissue dilatation, respiration increasing, and blood pressure increasing [67].

Most cases of food poisoning due to tyramine are associated with cheese followed by other foods such as pickled herring, meat products, avocados, soy sauce, miso, chicken livers, beef livers,and caviar [68]. Brink et al. [69]have reported that levels of histamine at more than 500 ppm are toxic to human.

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The histamine in food at 8–40 mg can cause slight poisoning, and 1080 ppm of tyramine is considered very harmful to adults [69]. On the other hand, with intake of monoamine oxidase inhibitor (MAOI) drugs, tyramine concentration at 100–250 ppm can cause hypertension. It has been shown that phenyethylamine at dose of 3 mg can significantly produce symptoms of migraine [70].

Moreover, histamine plays a major role in the metabolic system, like nerve functions and blood pressure regulation. Specifically, by binding to the cardiovascular system, Vasodilatation and Hypotension, and cell membrane receptors, it affects several secretory glands, such as thesecretion of gastric acid.[71-72]. It may also lead to some neurotransmission disorders and cause headache, flushing, gastrointestinal disorders, and edema by increasing blood vessel dilatations [73-74]. Histamine intoxicates when orally taken in amounts of 8 mg and above [75]. Individuals generally have lower intestinal oxidase enzyme activities according to the healthy persons, as they hold the gastrointestinal problems such as gastritis, stomach and colonic ulcers [76, 74].

Polyamines

Polyamines: Biosynthesis[77]

Polyamines are synthesized within all living cells, in eukaryotes, polyamine synthesis begins with ornithine, which is synthesized through the urea cycle from arginine. The decarboxylationof ornithine catalyzed by Ornithine Decarboxylases (ODC) is the rate-limiting step in polyamine synthesis. Spermidine and spermine are then synthesized by the sequential addition of aminopropyl groups donated from Decarboxylated S-adenosylmethionine (dc- SAM), which is converted from S-adenosylmethionine (SAM) by the enzymatic activities of Adenosylmethionine decarboxylase (AdoMetDC).

Decarboxylated S-adenosylmethionine (dc-SAM), which is used as a substrate for the aminopropyltransferases, spermidine synthase (SpdSy) and spermine synthase (SpmSy), which

are constitutively expressed and active as homodimers.[78] The aminopropyltransferases catalyze the synthesis of Spd from Put and subsequently Spm from Spd. Both Spd and Spm are N 1- acetylated by the highly inducible polyamine catabolizing enzyme spermidine/spermine N 1- acetyltransferase. The acetylation of the polyamines Spd and Spm converts the molecules into substrates of constitutively expressed N 1-acetyl polyamine oxidase, which catabolizes acetylated Spm to Spd and acetylated Spd to Put. The acetylated forms of Spd and —Spm can also be exported from the cell. The most recently discovered polyamine catabolizing enzyme is spermine oxidase, which uses Spm as a substrate producing Spd, 3-aminopropanal and H_2O_2.[78]

Polyamines: Physiological Significance[77]

There are 3 major types of polyamines in the body known as, Putrescine (PUT), Spermidine (SPD), and Spermine (SPM). Under the physiological conditions[77], are strong flexible polycations exhibiting 2, 3, or 4 positive chargers, respectively. They can interact with negatively charged macromolecules such as nucleic acids, phospholipids, and proteins. Which ionic interactions are reversible, and lead to the stabilization of DNA, RNA, membranes, and some proteins. These revealed that polyamines are important in the growth, maintenance, and function of normal cells. These participate in several biological processes in humans, some of which are favorable and others injurious. In mammals, polyamines are involved in the most important physiological process. Cell proliferation and viability, nutrition, fertility, as well as nervous and immune system. In some instances where altered synthesis or metabolism of polyamines lead to several types of pathological conditions

Polyamines: Toxicity

Polyamines (Table 1) are known to lead to low-dose colon cancer by affecting the cell developments and differentiation [79-80]. In addition to them, putrescine, cadaverine, spermine, and spermidine were also found to induce apoptosis and inhibit cell proliferation. The high-dose

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putrescine was found to induce apoptosis and prevent the spread [81-82]. This putrescine effect pertains to increasing the nitric oxide synthesis, inhibiting the redox reactions and bindingdirectly to the carcinogenic agents [82].

Polyamines: The Potential Indicators for Deterioration of Food, Food Products of Beverages

BAs (Table 1) can be used as spoilage indicators for different meat products. In particular, the biological amines index (BAI = histamine + putrescine + cadaverine + tyramine) and quality index (QI) = (histamine + putrescine + cadaverine)/(1 + spermidine + spermine) have been used to evaluate the freshness of meat products[12]. BAs formation are species specific. Putrescine and cadaverine have been detected in significant concentrations in fermented meat and fish[12]. Cadaverine was reported to be a reliable spoilage indicator of poultry meat, whereas histamine has been regarded as an index of the fish quality, particularly dark-muscle fish.

Tyramine is reported to cause food intoxication commonly associated with ripened cheeses, affecting health due to its capacity to potentiate sympathetic cardiovascular activity by releasing noradrenaline, called –cheese reaction‖. Histamine, putrescine, cadaverine, tyramine, 2-phenylethylamine, and tryptamine are often detected in fermented products. In addition, the level of BAs in alcoholic beverages (*i.e.* wine and beer) has received much attention since ethanol and acetaldehyde can increase the risk to human health by retarding the enzymes responsible for detoxification.

Patients with chronic kidney failure show high plasma polyamine oxidase activity, which causes an increase in spermine and spermidine catabolism and the accumulation of toxic *acrolein*. In such patients, a high polyamine (PA) might be harmful. Spermine and spermidine are mainly found bound to polyanionic molecules such as DNA, RNA, ATP, and phospholipids.[83] Cadaverine and putrescine within the periodontal environment have demonstrated cell signalling interfering abilities, by way of leukocyte migration disruption. The polyamines spermine and spermidine in tumour cells have been shown to inhibit cellular apoptosis, effectively prolonging tumorigenesis and continuation of cancer within the host. Polyamine degradation products such as acrolein have been shown to exacerbate renal damage in chronic kidney desease patients. Thus, the use of such molecules has merit to be utilized in the early indication of such diseases inpatients.[83]

Interplay Between the Mono/Diamines with Polyamines

The presence of putrescine and cadaverine along with tyramine and histamine in food has been found to be responsible for their toxic effect on human [84]. Furthermore, cadaverine, putrescine, spermine, and spermidine can form carcinogenic nitrosoamines by reacting with nitrite [85]. Currently no data is available for the dose–response effects of putrescine or cadaverine on human.

The potentiation of histamine's toxic effect may also be explained by putrescine and cadaverine facilitating the passage of histamine across the small intestine, thus increasing its rate of absorption into the blood stream. In addition, putrescine and cadaverine can react with nitrites and produce nitrosamines (putrescine yields nitrosopyrrolidine and cadaverine nitrosopiperidine), compounds known to be carcinogenic. Putrescine (which physiological concentration in the colonic lumen is normally in the milimolar range) has also been indicated directly involved in the oncogenic process. An association has also been reported between high intakes of dietary putrescine, along with the polyamines spermidine and spermine, and the risk ofdeveloping colorectal adenocarcinoma.

Biogenic Amines in Beverages, Food Products and Agriculture [86, 87]

Higher levels of biogenic amines are present in red berries and wines. In the berries and wine of these two varieties, Putrescine and histamine were most biogenic amines. Red fruits and wines have more anthocyanins, which tend to be high in antioxidant activity compared with whites.Red and white berries and wine had similar levels of polyphenols, but different metabolite profiles depending on grape varieties. Polyphenols, anthocyanins, antioxidant activity, and biogenic amines are present

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in white (Albana) and red (Lambrusco) grape berries, as well as wines from the Emilia-Romagna area (Italy) produced using conventional, organic, and biodynamic agricultural and oenological approaches.

Discussion

Based on review on Biogenic amines including monoamines and polyamines, further investigation on novel methods for isolation and estimation of biogenic amines is required from banana plant.

For that, prior step for removal of proteins and debris from banana peels (containing CNS active monoamines such as dopamine, serotonin and epinephrine) is required.

Conclusion

Elevated level of biogenic amines within the human body provokes diverse clinical events, although when treated within the therapeutic regime of the concerned dosage regime of suitable biogenic amine may restore the physiological events to be observed. In addition, in order to elicit adequate biological action, it is necessary to control the level of specific biogenic amine within a living organism.

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