

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

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Abstract

Biogenic amines, including dopamine, serotonin, and histamine, play critical roles in regulating physiological and neurological processes. Increasing evidence suggests that herbal and waste-derived sources of these amines may offer significant neuroprotective and therapeutic potential. This paper explores the biosynthesis, extraction, and characterization of biogenic amines from plant-based and organic waste materials, emphasizing their biochemical mechanisms and potential applications in managing neurodegenerative disorders. The study also highlights the environmental and economic advantages of utilizing waste-derived compounds for pharmaceutical and nutraceutical development. Through an interdisciplinary approach combining neurochemistry, pharmacology, and sustainable resource utilization, this work aims to advance understanding of how biogenic amines from natural and waste sources can be harnessed for neuroprotection and therapy.

Keywords: Biogenic Amines, Herbal Sources, Waste-derived Compounds, Neuroprotection, Neurodegenerative Diseases, Dopamine, Serotonin, Sustainable Bioresources, Therapeutic potential, Nutraceuticals.

Introduction

Biogenic Amines as Cell-Protective Mediators

Biogenic amines, including monoamines such as dopamine, norepinephrine, epinephrine, and serotonin, serve crucial roles as neurotransmitters and are deeply involved in the regulation of neural processes. These signaling molecules are not exclusive to animal systems; they are widely distributed across biological kingdoms, including plants, animals, and microorganisms [1-4]. In animals, these amines can exert both neuroprotective and neurotoxic effects, depending on their concentration and context [3]. Particularly within microbial systems, polyamines contribute to oxidative stress resistance, playing a defensive role against reactive oxygen species during host-pathogen interactions [4]. Given their diverse physiological effects and chemical versatility, biogenic amines have emerged as key molecules for further exploration—especially regarding their selective isolation and utilization for therapeutic applications in neurodegenerative and neurological disorders.

Physical and Chemical Properties of Biogenic Amines

The physical and chemical characterization of biogenic amines has been extensively studied, focusing on aspects such as vapor pressure, phase equilibria, and other thermodynamic parameters essential for accurate physicochemical assessment [5]. These compounds are organic nitrogen-containing molecules of low molecular weight, typically classified into three structural categories: (i) aromatic and heterocyclic amines (e.g., histamine, tryptamine, tyramine, phenylethylamine, and serotonin), (ii) aliphatic diamines, triamines, and polyamines (e.g., putrescine, cadaverine, spermine, spermidine, and agmatine), and (iii) aliphatic volatile amines (e.g., ethylamine, methylamine, isopentylamine, and ethanolamine). From a functional group perspective, they are further divided into monoamines (such as phenylethylamine, tyramine, methylamine), diamines (such as histamine, tryptamine, serotonin, putrescine, and cadaverine), and polyamines (such as spermine, spermidine, and agmatine). These amines demonstrate a range of physicochemical proper-

ties, including diverse log P values, pKa values, and solubility in water [6]. Consequently, they can behave as basic, acidic, or amphoteric molecules depending on their structural features and environmental conditions [6].

Reviews of Literature

Biogenic amines such as dopamine, epinephrine, and norepinephrine are monoamines that occur in both animal and plant systems.

Dopamine

Dopamine is found in the brain of animals and in banana species in plants [1, 2]. It has a Log P of -0.98 and a pKa of 9.27 and 10.01 [6]. The separation methods used include solid-phase extraction (SPE) and liquid-liquid extraction (LLE) [6]. Dopamine acts as a neurotransmitter in animals and affects photosynthesis in plants. However, it can exert mitochondrial complex I inhibition, leading to neurotoxicity [3]. Therapeutically, dopamine is important in Parkinsonism, depression, and other central nervous system (CNS) disorders.

Epinephrine

Epinephrine is also found in animal brains and in *Lemna paucicostata* and banana species, has a Log P of -1.37 and pKa values of 8.91 and 9.69 [1, 2, 4, 6]. High-performance liquid chromatography (HPLC) is commonly used for its separation [6]. As a neurotransmitter, epinephrine regulates cytoplasm movement, ion permeability, and membrane potential in plants [4]. Toxic effects include long-lasting skin rashes and dyspnea, while its therapeutic use includes treatment of anaphylaxis [7].

Norepinephrine

Norepinephrine is similarly present in animal brains and plants such as *Lemna paucicostata* and banana species, exhibits a Log P of -1.24 and -1.46 and pKa values of 8.85 and 9.5 [1, 2, 4, 6]. It is commonly separated using GC-MS [4]. Norepinephrine is a neurotransmitter that, in plants, promotes flowering under specific photoperiodic regimes. Toxicologically, it may cause uncontrolled hypertension, but therapeutically it is applied in the treatment of cardiac arrest with profound hypotension [8].

Serotonin

Serotonin is a diamine, is found in animal brains and in banana species [9, 1, 2]. It has a Log P of 0.21 and a pKa of 9.31 and 10 [6]. It is isolated using on-line microdialysis techniques [6]. As a neurotransmitter, it regulates plant growth and stress response [10]. Excess serotonin may lead to serotonin syndrome and serves as a neuromodulator [11].

Histamine

Histamine is also a diamine, occurs in fermented animal products and banana plants [12, 1, 2]. It shows a Log P of -0.70 and pKa values of 9.68 and 5.88 [13]. Functionalized silica materials are used for its separation [14]. In animals, histamine acts as an inflammatory mediator, while in plants it is involved in cellular responses to stress [15]. Histamine can cause scombroid poisoning in humans and is involved in regulating physiological processes [9].

Putrescine

Putrescine is another diamine, is found in fish, dairy products, and in wheat plants [12, 16]. It has a Log P of -0.70 and pKa of

10.51 [13]. Functionalized silica materials are used for its separation [13]. Putrescine improves animal growth and positively influences plant development [17, 18]. It potentiates the toxicity of other amines by inhibiting detoxifying enzymes, and it is essential for angiogenesis [9].

Cadaverine

Cadaverine is also a diamine, is present in beef and barley seedlings [19]. It has similar separation properties and contributes to plant stress tolerance and antioxidant mechanisms [14]. It also potentiates histamine's toxicity due to enzyme inhibition and has known toxic effects [9, 20].

Spermine

Spermine is a polyamine, is found in mice and in *Arabidopsis* species [21, 1, 2]. It shows a Log P of -0.7 and pKa of 10.8 [22]. Functionalized silica materials are used for extraction [14]. Spermine levels decrease with prostate cancer progression, and it increases plant resistance to stress [23]. Acrolein toxicity, a product of spermine metabolism, is a known concern [24]. Spermine also exhibits neuroprotective effects [3].

Biogenic Amine-Based Identification, Detection and Quantification

There are distinct methods available for Separation and identification of biogenic amines. 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 medium color and pH [25]. Most detection methods for BAs have been developed based on chromatography technology. HPLC with fluorescence detection, UV detection, or mass spectrometry detection after derivatization of benzoyl chloride, dansyl chloride, and o-phthalaldehyde have been successfully used [26-28].

The high-performance liquid chromatography (HPLC), gas chromatography (GC), thin-layer chromatography (TLC), ion exchange chromatography, biosensors, and capillary electrophoresis (CE) are the method used for detection of BAs [29-34]. It has been applied to wines, soybean paste, and pepperoni sausage to determine BA levels [35, 36]. To provide a chromophore for UV or fluorescence detection, their polarity needs to be reduced. This process is generally done by derivatization [37]. Dansyl chloride, benzoyl chloride, and o-phthalaldehyde are generally used for derivatization [38-40]. Extraction is one practical step used in most BA detection techniques.

Tang et al. (2021), have reported the detection of BAs in sufu through HPLC with solid-phase extraction (SPE) and pre-column derivatization [41]. HPLC with direct derivatization of acid extract has been used to quantify BAs in cheese [38]. To determine BAs in Port wine and grape juice, Fernandes and Ferreira have employed gas chromatographic-mass spectrophotometric method in selected ion-monitoring mode using heptafluorobutyric anhydride as a derivatization reagent [42]. Capillary electrophoresis with conductometric detection has been used to detect BAs in food without any derivatization steps [43].

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 and wine. Dadakova et al. have demonstrated a rapid ultra-performance liquid chromatography (UPLC) to detect Bas [44-46]. Ultra-high pressure liquid chromatography-electrospray tandem mass spectrometry (UHPLC-ESI- MS/MS) has been used to determine BAs in Cheonggukjang [47]. In addition, an enzyme sensor array has been proposed to simultaneously determine several types of BAs with less time required [48].

Important Chemical Reactions and Biological Actions of Biogenic Amines

Chemical Reactions

Heat Treatment of Biogenic Amines (Smith & Kirshner, 1960)
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 was proposed to be the addition of amine to dehydroalanine, suggesting that the latter may originate, at least in some proteins, from serine residues [49]. Prolonged heating, higher temperatures, higher pH, and increased amine concentration all improved the yield of the new amino acids [49]. 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 [50].

Derivatization of Biogenic Amines (Akmese & Asan, 2017)

The optimal conditions for the derivatization reaction of biogenic amines (histamine, tyramine, putrescine, 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 (Wójcik et al., 2021)

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 (Connil et al., 2002)

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 circula-

tion, 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 [51]. Symptoms of poisoning can appear within several minutes to 3 h after ingestion of fish containing histamine at levels higher than 1 mg/g [52]. Tyramine, phenylethylamine, and tryptamine are mainly causing hypertension, headache, pupil dilatation, palpebral tissue dilatation, respiration increasing, and blood pressure increasing [53].

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 [54]. Brink et al. (1990) have reported that levels of histamine at more than 500 ppm are toxic to human [55]. The histamine in food at 8–40 mg can cause slight poisoning, and 1080 ppm of tyramine is considered very harmful to adults [55]. 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 phenylethylamine at dose of 3 mg can significantly produce symptoms of migraine [56].

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 the secretion of gastric acid. [57, 58]. It may also lead to some neurotransmission disorders and cause headache, flushing, gastrointestinal disorders, and edema by increasing blood vessel dilatations [59, 60]. Histamine intoxicates when orally taken in amounts of 8 mg and above. 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 [61, 60].

Polyamines

Polyamines: Biosynthesis (Sarvananda et al., 2023)

Polyamines are synthesized within all living cells, in eukaryotes, polyamine synthesis begins with ornithine, which is synthesized through the urea cycle from arginine. The decarboxylation of 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. 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 [62]. 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 H₂O₂ [62].

Polyamines: Physiological Significance (Sarvananda et al., 2023)

There are 3 major types of polyamines in the body known as, Putrescine (PUT), Spermidine (SPD), and Spermine (SPM). Under the physiological conditions, are strong flexible polycations exhibiting 2, 3, or 4 positive charges, respectively [63]. 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 [64, 65]. In addition to them, putrescine, cadaverine, spermine, and spermidine were also found to induce apoptosis and inhibit cell proliferation. The high-dose putrescine was found to induce apoptosis and prevent the spread [66, 67]. This putrescine effect pertains to increasing the nitric oxide synthesis, inhibiting the redox reactions and binding directly to the carcinogenic agents [67].

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

BAs 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 [9]. BAs formation are species specific. Putrescine and cadaverine have been detected in significant concentrations in fermented meat and fish [9]. 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 polyam-

ine 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. Cadaverine and putrescine within the periodontal environment have demonstrated cell signaling interfering abilities, by way of leukocyte migration disruption [22]. The polyamines spermine and spermidine in tumor 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 disease patients. Thus, the use of such molecules has merit to be utilized in the early indication of such diseases in patients [22].

Interplays 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 [68]. Furthermore, cadaverine, putrescine, spermine, and spermidine can form carcinogenic nitrosoamines by reacting with nitrite [69]. 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 polyamine's spermidine and spermine, and the risk of developing colorectal adenocarcinoma [70-72].

Biogenic Amines in Beverages, Food Products and Agriculture (Sørensen et al., 2018), (Tassoni et al., 2014)

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 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 [73-76].

Discussions

This review highlights the neuroactive potential of biogenic amines, particularly monoamines and polyamines, derived from herbal and agro-waste sources. Among these, banana peels—a notable waste resource—contain central nervous system (CNS) active monoamines such as dopamine, serotonin, and epinephrine. However, there remains a critical need to develop novel and selective methods for the efficient isolation, purification,

and quantification of these compounds. Effective removal of interfering substances like proteins and cellular debris is a prerequisite for improving yield and accuracy in their extraction. Advancing such methodologies could unlock the therapeutic potential of biogenic amines from sustainable plant-based sources.

Conclusions

Biogenic amines from herbal and waste-derived sources hold significant promise for neuroprotective and therapeutic applications. Nevertheless, elevated concentrations of these amines in the human body can trigger adverse clinical effects. Therapeutic use requires careful modulation of their dosage and concentration to ensure efficacy while minimizing toxicity. Therefore, precise monitoring and control of biogenic amine levels are essential to achieve targeted biological responses. Harnessing these compounds from natural and sustainable sources like banana peels offers an innovative and eco-conscious route for future therapeutic development.

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The authors declare no conflict of interest.

Consent to Participate, Ethical Approval and/or Institutional Review Board (IRB)

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