



Recent advances of electrochemical and optical point-of-care biosensors for detecting neurotransmitter serotonin biomarkers

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ABSTRACT

Since its discovery in 1984, the monoamine serotonin (5-HT) has been recognized for its critical role as a neuromodulator in both the central and peripheral nervous systems. Recent research reveals that serotonin also significantly influences various neuronal activities. Historically, it was believed that peripheral serotonin, produced by tryptophan hydroxylase in intestinal cells, functioned primarily as a hormone. However, new insights have expanded its known roles, necessitating advanced detection methods.

Biosensors have emerged as indispensable tools in biomedical diagnostics, enabling the rapid and minimally invasive detection of target analytes with high spatial and temporal resolution. This review summarizes the progress made in the past decade in developing optical and electrochemical biosensors for serotonin detection. We evaluate various sensing strategies that optimize performance in terms of detection limits, sensitivity, and specificity. The study also explores recent innovations in biosensing technologies utilizing surface-modified electrodes with nanomaterials, including gold, graphite, carbon nanotubes, and metal oxide particles. Applications range from in vivo studies to chemical imaging and diagnostics, highlighting future prospects in the field.

1. History and importance of serotonin

Serotonin, a monoamine neurotransmitter derived from tryptophan and known as 5-hydroxytryptamine (5-HT), plays a crucial role in various physiological processes. The discovery of serotonin as a fundamental neurotransmitter is a compelling story, marked by the collaborative efforts of multidisciplinary research groups (Fig. 1). In 1868, Ludwig and Schmidt were the very early research scientists to describe their research observation on the physiological action of serotonin is being studied (Ludwig and Schmidt, 1868). These early investigators observed that the arterial infusion of defibrinogenated blood led to an increase in vascular resistance in the muscles of injected dogs. The earliest significant research on serotonin was conducted by Vittorio Erspamer in 1935 in Rome, Italy. Erspamer discovered that a chemical compound extracted with acetone from enterochromaffin cells in the mucosal membrane of the gastrointestinal tract induced smooth muscle contractions in the rat uterus. Through a series of fundamental chemical experiments, he hypothesized that this compound was an indolic substance, which he named 'enteramine.' (Erspamer and Vialli, 1937; Nichols and Nichols, 2008). Irvine Page and his laboratory had first

discovered that the vasoconstrictor substances in the blood and a vasoconstricting substance were immediately produced when blood coagulated. First, serotonin was extracted and refined by Arda Green then Maurice Rapport, a gifted organic chemist; they separated serotonin from around 900 L (liter) of blood serum fluid taken from over 200 kg (kilograms) of beef blood" (Colowick, 1958; Rapport et al., 1948b). In 1948, a purified crystal substance become known as serotonin. The name "ser" comes from the truth that it was originated in the serum and restricted before elevated in tone ("tonin") in the bloodline vessels (Nichols and Nichols, 2008; Rapport et al., 1948a). In 1951, Abbott Laboratories' Hamlin and Fischer chemically produced 5-HT, a hypothesis made by Rapport based on the chemical structure of the serotonin interpretive technique (Rapport et al., 1949). The letter on Erspamer and Asero in 1952 emphasized synthetic serotonin, and it was explicitly similar to 'enteramine', which was extracted as a pure state from biological resources (Erspamer and Asero, 1952a). Thus far, serotonin's function in the peripheral vascular system has only been identified as contracting smooth muscle and narrowing blood channels.

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1.1. Structure of serotonin

In 1949, Dr. Betty Twarog, while pursuing her doctorate at Harvard University, examined the membrane of smooth muscle for her research to classify the neurological molecule that controlled catch in *Mytilus*. She found that it contracted the muscle, then created an exceptionally sensitive biological assay for operating serotonin hard-shell clam's distinct heart *venus mercenaria* also known as ("quahogs"). Further, she performed acetone extracts from several tissues found in mammals, including the brain, and counted the estimated volume of serotonin in the tissues while performing in Irvine Page's lab at the Cleveland Clinic (Twarog, B. M. and Page, I. H., 1953a). In 1953 Irvine Page's surprise, she discovered easily detectable serotonin levels in the brains of mice, rabbits, and dogs (Whitaker-Azmitia, 1999). While Dr. Albert Hofmann reported in 1943 the discovery of serotonin in the brain used at Sandoz Laboratories in Basel, it was ultimately lysergic acid diethylamide (LSD-25) that was shown to have powerful properties that cause mental modification (Novak, 1997). For the first time, Werner A. Stoll systematically investigated LSD in humans at the Psychiatric Clinic, Zurich University (Stoll, 1947). The point was to learn that tryptamine fragments are allied within the LSD structure and the serotonin scaffolding. First put forth in 1954, Woolley and Shaw postulated that "a serotonin interference with in the brain causes mental illnesses such as schizophrenia is responsible for mental disturbances caused by LSD" (Woolley and Shaw, 1954).

In 1955, the invention of a spectro-photo-fluorometer represented the beginning of the technological development of analytical techniques for serotonin detection. This new optical technique provided more simplicity and more throughput than isolated-tissue bioassay by allowing for the sensitive measurement of monoamine levels, including serotonin and other neurotransmitters (Bowman et al., 1955). In 1962, Falck-Hillarp et al. reported the first technique that made serotonin viewing in situ possible because yellow-green color quinoline molecules formed during freezer drying tissue exposure to formaldehyde vapor allowed the imaging of serotonin (Falck et al., 1982). Further, Dahlström and Fuxe employed this technique in 1964 to image and visualize neurons producing serotonin in the rats brain, grouping them into nine clusters denoted from B1 to B9 (Dahlström and Fuxe, 1964). In the early 1970s, the first electrochemical and microanalysis techniques were reported to assess serotonin levels in living, acting animals using functional MRI (magnetic resonance imaging) and PET (positron emission

tomography) (Kissinger et al., 1973).

The first results report of serotonin transportation and metabolism in the cerebral cortex of humans were obtained utilizing MRI and PET methods for clinical and scientific studies on the serotonergic pathway (Krämer et al., 2011). As we know, serotonin plays several crucial roles in the brain's normal functioning, including modulating mood states, appetite, sexual wellness, memory, feeling, sleep, panic attacks, neuro-endocrine impacts, healing from wounds, digestion, and many others. The receptors that respond to serotonin are comprehensively characterized across the nervous system, and numerous essential structures are required for fundamental mental action. One of the first neurotransmitter systems is serotonin, which arises early in evolution. Its role as a model has persisted and even grown to encompass different evolutionary tree branches.

Numerous scientific methods, including mass spectrometry, capillary electrophoresis, ELISA, fluorimetry, radioimmunoassay, HPLC-ECD, chemiluminescence, enzyme immunoassay (Chavan et al., 2021; Sharma et al., 2018), and many other have been used to identify serotonin. However, these traditional methods are inconvenient for routine testing and inappropriate for quick detection since they are laborious, time-consuming, and frequently require sample pretreatment. As an alternative, an electrochemical and optical serotonin measuring technique provides remarkable benefits for ongoing real-time monitoring because of its many advantages, including high temporal clarity, quick reaction kinetics, ease of downsizing, and high sensitivity. The benefits of electrochemical and optical serotonin sensors include excellent stability, wide linear response, high sensitivity, and repeatability. An additional significant benefit is the low-cost measurements. As such, during the past few decades, there has been a lot of interest in developing optical and electrochemical sensors for detecting serotonin.

Numerous research studies have been published using chemically modified nanoparticles, nanomaterials, and electrodes to detect serotonin. In 2022, Liu et al. summarized in-depth review of the characteristics of the surface coating materials and the interactions at the interfaces of these microelectrodes, as well as a survey of some of the literature that has been published on the use of microelectrodes with various carbon-based coatings to detect monoamine neurotransmitters from 1953 to 2021 (Liu et al., 2022). Additionally, researchers have explored the principles of electron transmission in carbon nanomaterials and examined the fabrication and application of various 2D graphene-based electrochemical biosensors. Their work has highlighted

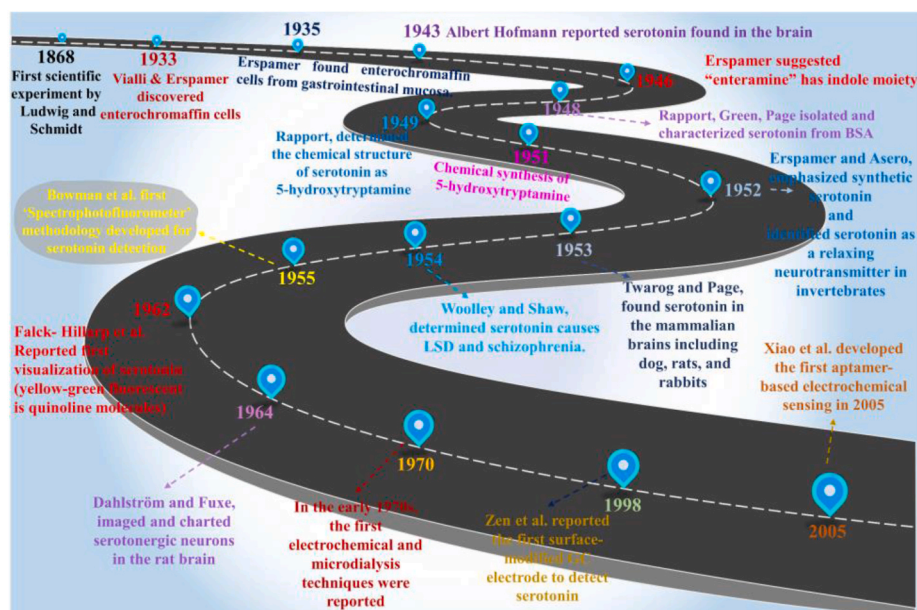


Fig. 1. Comprehensive overview of serotonin discovery and established methodologies for serotonin biosensing were presented.

significant advancements in the development of nanomaterial-based electrochemical biosensor devices, which are used to detect biomedically important analytes commonly present in pharmaceutical, biological, clinical, and medical fluids. These innovations have expanded the capabilities of biosensors, enhancing their sensitivity and specificity in identifying critical biomarkers. (Azzouz et al., 2019; Venkatesan et al., 2024). It is difficult to put these findings together in a review article because most research articles do not include a critical comparison with the published work. Our comprehensive presentation covers the most efficient and promising electrical and optical techniques for serotonin detection, which include the use of carbon nanomaterials and nanotubes, field-effect transistor (FET), conductive nanomaterials, nanoparticles, electrodes with surface modifications, enzymatic and electrochemical oxidation of serotonin. We are not aware of any previous review study that has been published that summarizes the specifically optical and electrical determination methods for serotonin.

2. Biosynthesis and metabolic functions of serotonin

Serotonin was first discovered in a variety of organisms in the 1940s, including plants, mammals, and fungi. It is possible to distinguish between two major serotonin pools: brain serotonin, primarily produced in the brainstem, and peripheral serotonin. Since serotonin cannot cross the blood-brain barrier, different pools of this chemical have different biological effects (Berger et al., 2009b). L-tryptophan, an important amino acid that initiates the serotonin metabolic pathway, is the only precursor molecule involved in serotonin synthesis. The biological pathway for serotonin production has two steps in the metabolic pathway (Pourhamzeh et al., 2021) Fig. 2. Initially, serotonin synthesis in both locations implies the conversion of the L-tryptophan to 5-HTP (5-hydroxytryptophan) via an enzyme-dependent mechanism that is rate-limiting (tryptophan hydroxylase, or TPH), which is expressed in the brain and peripheral region by two distinct genes, *Tph-1* and *Tph-2*, respectively. However, serotonin is produced through the subsequent decarboxylation of 5-HTP through AADC (aromatic amino acid decarboxylase) and VMAT-2 (vesicular monoamine transporter isoform-2) collect produced serotonin and stored in the neurotransmitter vesicles or (synaptic vesicles). Through Ca^{2+} -dependent exocytosis, serotonin is released in the cleft of synaptic neurons upon an action potential. It can control the downstream showing pathway with post- and pre-synaptic

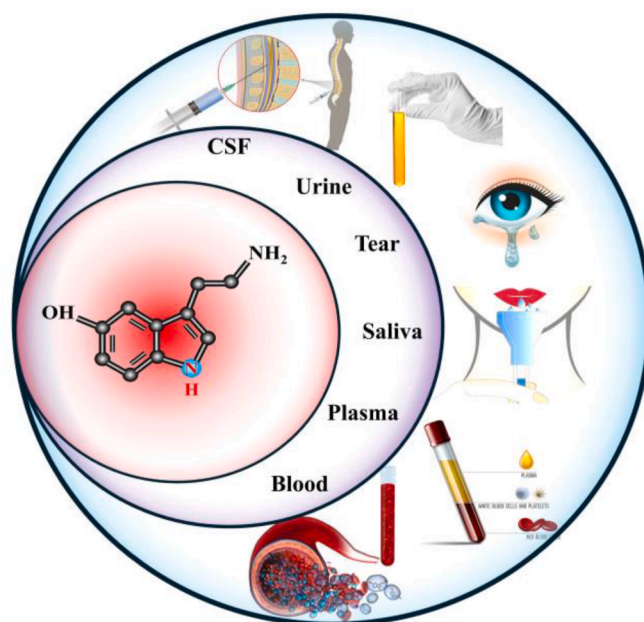


Fig. 3. Extensive research has been conducted on many biological sources of serotonin to enable effective point-of-care testing.

receptors. It can also control its extracellular level by reabsorbing through the serotonin transporter (SERT) located in the soma and axon terminals of serotonergic neurons. Furthermore, 5-HIAA (5-hydroxyindoleacetic acid) is possibly produced with the metabolism of serotonin by aldehyde dehydrogenase and monoamine oxidase-A (MAO-A) (see Fig. 3).

Serotonin metabolism is mainly influenced by the outer mitochondrial membrane enzyme MAO, which has found two distinct molecular subtypes: MAO-A and -B (Bortolato et al., 2010). Both subtypes are commonly found in the brain and surrounding peripheral tissues, but they differ in specific manners, such as in species-related variations, regarding how much of each subtype is found in which organs and cell types (Nagatsu, 2004). First, a rate-limiting reaction with TPH, an enzyme, catalyzed the formation of 5-HT. Next, TPH is primarily found in the gut enterochromaffin cells and brainstem. It is a member of the aromatic amino acid hydroxylase superfamily, strictly associated with tyrosine hydroxylases and phenylalanine (Grenett et al., 1987; Walther et al., 2003).

In humans, enhancing tryptophan concentrations may increase serotonin synthesis; conversely, lowering tryptophan accessibility can drastically decrease serotonin synthesis (Gibson, 2018). Sainio et al. and coworkers reported in 1996 that the tryptophan synthesis increasing serotonin, a 6g dose (almost daily 6-time dietary intake) is sufficient to double the rate of serotonin synthesis and saturate tryptophan hydroxylase (Sainio et al., 1996). Blier et al. and Diksic et al. reported that the serotonin biosynthesis rate in normal male brains was 52 % greater than in ordinary females (Blier and de Montigny, 1994). Both male and female subjects' measurements in cerebrospinal fluid (CSF) investigation indicate that the brain serotonin metabolism rate is higher in females and the occurrence of significant unipolar depression than man (Nishizawa et al., 1997; Weissman and Olfson, 1995). Serotonin neurons are found only in amniotes' raphe region of the hindbrain, whereas serotonin cell bodies found in pretectal regions and the basal forebrain in amniotes, including teleosts (Höglund et al., 2019). Likewise, in zebrafish, serotonin cells express TPH1 (TPH1a and TPH1b) and TPH3, respectively, while raphe and pretectal TPH-2 are expressed by hypothalamic and diencephalic serotonin cells.

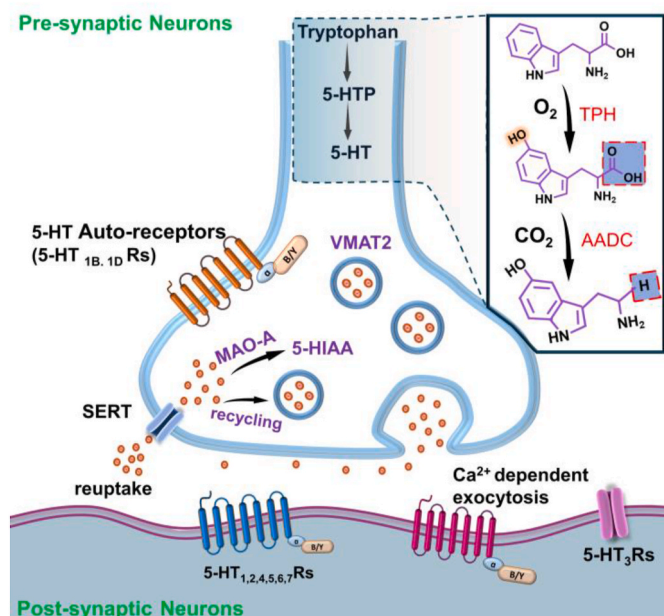


Fig. 2. Schematic illustration of biosynthesis and metabolism of serotonin.

2.1. Serotonin regulator background in CNS

In the CNS, serotonin modulates various behavioral processes, motor and cortical functions of the human body. Surprisingly, the less than one million CNS serotonergic neurons that secrete serotonin originate from the brain stem's primary raphe nuclei, constituting merely 5% of the entire body's serotonin. A substantial 95 % of serotonin is found in the peripheral system, which regulates several physiological processes such as autonomic, paracrine, or hormones. Additionally, the gastrointestinal system's enterochromaffin cells and gut neurons are where its production is dispersed (Berger, M. et al., 2009; Julius, 1991). In the biosynthesis of serotonin outside the CNS, 98% is preserved in dense granules within the platelets, and very little serotonin is found within the megakaryocytes. Serotonin is released into the bloodstream along with platelet-derived growth factor (PDGF) and other compounds contained in platelets when artery walls are broken. Megakaryocytes are the only cells in the bone marrow that can process serotonin and are the precursors of the blood platelets (Liu and Yang, 2006). Approximately 2% of the blood serotonin is available as a hormone (El-Merabhi et al., 2015). In addition to adenosine diphosphate and bivalent calcium ions, serotonin is saved in platelets as dense granules at a concentration of 65 mM (Holmsen and Weiss, 1979). When hemostatic difficulty lies, platelets release serotonin into the external environment, acting independently and/or with neighboring platelets (Mammadova-Bach et al., 2018). In past studies, only serotonin concentrations in dense granules have previously been reported in neurological research, this was then applied to determine the amount of serotonin contained in one platelet. Notably, Lee et al. further investigated the range of serotonin in one platelet. The dense granule diameter was 161 nm (Ogston, 2012), and each compact granule contained roughly 1.42×10^{-19} mol of serotonin particles. Each platelet comprises six compact, packed granules, resulting in 8.52×10^{-19} mol of serotonin per platelet (McNicol and Israels, 1999). The final range of serotonin in a one human platelet is 94.7 μ M, calculated by dividing this number by the average diameter of platelets, which is 9 fL (Lee et al., 2020).

2.2. Serotonin regulator background in PNS

In 1948, Rapport and laboratory coworkers found a vasoconstrictor chemical material in the blood (Erspamer and Asero, 1952b) and, after four more years, recognized that enteramine and serotonin were the same molecules, and soon after, Page and Twarog recognized serotonin in the mammal's brain (Twarog, Betty M and Page, Irvine H, 1953b). Just around 5% of the body's total serotonin is found in the cerebral cortex, but this finding led to the identification of serotonin as a crucial neurotransmitter molecule and sparked interest in controlling brain activities. In comparison, less than 95 % of its content was found in peripheral tissues (Amireault et al., 2013). In the PNS, most serotonin originates through enterochromaffin cells of the gut, and it can function in the GI tract, where serotonin accumulates in platelets during blood circulation and goes throughout blood coagulation (Rao and Gershon, 2018). The peripheral serotonin metabolism, serotonin, and serotonin receptors play a substantial role in controlling all virtual brain activities, and the pathogenesis of several psychological and neurological illnesses has dysregulated the serotonergic system (Roth and Xia, 2004). Interestingly, to understand serotonin, multiple functions with other peripheral cell types such as adipocytes (Stunes et al., 2011), liver (Li, H.-Y. et al., 2023a), pancreatic β cells (Kim et al., 2010), muscles (Liscia et al., 2012), macrophages (Vařicek et al., 2020), and osteoclasts (Durham et al., 2020) can produce serotonin. Although only seven of the fifteen distinct serotonin receptor groups (5-hydroxytryptamine receptors, or 5-Htrs) have been identified to date (5-Htr1 to 5-Htr7), the remaining serotonin-mediated communication in target cells is considerably more intricate (Kroeze et al., 2002). The ligand-gated ion channel among them is 5-Htr3, and the metabotropic G-protein coupled receptor subfamily has made more noteworthy discoveries (Noda et al., 2004).

However, a variety of G-proteins, nearly all of which are synthesized both inside and outside of the brain, are connected to different classes of 5-Htrs. (Pourhamzeh et al., 2022). We list the numerous ways serotonin produced in the periphery controls the balance of fats and carbohydrates in the brain by autopara and endocrine actions.

2.3. Serotonin in biofluids

One of the most important sources of life is whole blood, which offers vital data for tracking and controlling diseases and health illnesses information (Barbosa et al., 2005). Sampling can quickly produce complicated results in medical diagnostics instead of the difficulties and discomforts of collecting other body fluids, such as blood, plasma, interstitial fluid, CSF, tear, saliva, urine, and perspiration (Zhang et al., 2017). Stress harms health, potentially permanently altering the human immune system. As shown in Table 1, the summary of the serotonin range of concentrations is provided, together with information on the chemical's source and origin within the body, its weight and type, physiological levels in pertinent bodily fluids (such as cerebrospinal fluid (CSF), urine, blood, sweat, saliva, and platelets), and any associated medical disorders.

2.3.1. Levels of serotonin in CSF

Cerebrospinal fluid (CSF) originated from blood plasma, a colorless body fluid found within the surrounding tissue of every vertebrate's brain and spinal cord (Sakka et al., 2011). In the tela, choroidal of both the third and fourth ventricles, and the choroid plexuses of the imaginative cerebral ventricles, ependyma cells generate 60–75% of the CSF (Vigh et al., 2005). CSF releases 400–500 mL in adults per day and acts as a shock absorber cushion, supplying essential instinctive and immunological protection to the brain inside the skull (Sakka et al., 2011). Adults' CSF median volume is estimated to be 150 mL, of which 25 ml is found in the ventricles, and 125 ml is split between the cranial and spinal subarachnoid spaces. The normal range of serotonin in CSF was found 3.3 ± 3.4 ng/mL. CSF circulation and regulation is an ever-evolving phenomenon that is reliable for cerebral homeostasis. Due to a multidirectional flow in spinal cerebrospinal gaps and a univocal rostro-caudal movement in stomach cavities, CSF circulates from the release site to absorption. First and foremost, the systolic pulse wave in choroidal arteries indicates that CSF flow is pulsatile (Zervas et al., 1982). In young adults, CSF is replenished four or five times each 24 h. At the age of 77, they cut the CSF turnovers down to three times a day, which causes catabolites to build up in the brain and CSF and is also seen in several neurodegenerative illnesses (Johanson et al., 2008). The physiological values of CSF pressure dictate biological values, ranging from 3 to 4 mm Hg in newborns and 10–15 mm Hg in adults. In addition to the hydromechanical protection it provides for the central nervous system, the CSF is crucial for establishing and maintaining brain interstitial fluid homeostasis, which in turn affects how neurons function (Veening and Barendregt, 2010). The first promising CSF monoamine biomarkers of suicidality were the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA), the dopamine metabolite hom-vanillic acid (HVA), and the norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) (Hoertel et al., 2021; Virkkunen and Linnoila, 1990). The concentration level of the metabolite 5-HIAA in the CSF, which is higher in children than adults, can be used to measure serotonin activity in humans. It has been discovered that 5HIAA levels in the CSF of children diagnosed with autism spectrum disorder (ASD) accurately assess neuronal serotonin turnover (Hedner et al., 1986). Research from Linnoila et al. (1983) and Prato et al. (2008) is consistent with the theory that people with a history of suicidal thoughts and higher impulsivity are more likely to have reduced brain serotonin turnover, as measured by low 5-HLAA in CSF (Virkkunen et al., 1995). One of the more promising approaches to far has been to look into the possibility that suicidal conduct is related to the serotonergic system (Pandey, 1997). According to a 2006 research review by Mann et al., CSF levels of

Table 1

Summary of the normal concentration of serotonin in biological fluid.

Molecule type, & weight	Origin source	Body fluid	Normal range	Mortality range	Related health condition	Disease	Ref.
Serotonin (Neurotransmitter; $C_{10}H_{12}NO_2$, 176 Da. Amphiphilic)	Source: serotonergic neurons; origin: raphe nucleus of brainstem	CSF	0.141–0.65 ng/mL,	–	Mood regulation, Appetite, Antidepressant perceptions, Aggression, Anxiety, Cognition, Memory, Sexuality, Reward Processing, Learning, Attention, and Stability in Respiratory.	Alzheimer's disease Parkinson disease Psychiatric, and Neurologic diseases, Endocrine disorders.	Sinha et al. (2023)
		Urine	5–13 ng/24 h 881–7048 ng/ mL	–			
		Tear	2.74 ng/mL	–			Martin, X.D. and Brennan, M.C. (1994a) Adumitrăchioaie et al. (2019) Trabado et al. (2017) Steckl and Ray (2018) Kumar et al. (1990)
		Saliva	0.031–0.96 ng/mL	–			
		Human Plasma	14.09 –132.1 ng/mL	–			
		Blood	101–283 ng/ mL;	352.4 ng/ mL			
		Platelet	748.3 ± 448.3 ng/10 ⁹	–			

5-HIAA may have some predictive power for suicides in people with depression or anxiety, but only for optimistic values (Mann et al., 2006). Further investigation is required to reexamine this matter because, as of now, no study has looked at quantitatively synthesized results moderating the impact of the diagnosis on this relationship or whether there is a meaningful correlation between CSF levels of 5-HIAA and suicide attempts.

2.3.2. Levels of serotonin in urine

Urine has been commonly used as a 'favored' biofluid among metabolic biomarker discovery. (Erdbrügger et al., 2021). Urine is a clear, sterile, amber-colored fluid that is produced by the kidneys in mammals. It is a chemically complicated biological fluid that is simple to obtain in large quantities and is largely free of interfering proteins or lipids (Frutiger et al., 2021). However, metabolic breakdown products from different diets, drinks, medicines, endogenous waste metabolites, environmental pollutants, and bacterial by-products are commonly found in urine. The kidneys remove excess water, carbohydrates, and other chemicals from the blood as well as soluble wastes (Bouatra et al., 2013). MAO primarily metabolizes serotonin in the kidneys, liver, lungs, and intestines to 5-hydroxyindole-3-acetaldehyde (5-HIAL). Aldehyde dehydrogenase (ADH) can either oxidatively determine this intermediate aldehyde to 5-hydroxyindole-3-acetic acid (5HIAA) or decrease it to 5-HTOL. The final result of this process is that 5-HIAA is eliminated in free-form urine, while 5-HTOL, which is more lipophilic, is conjugated with sulfuric or glucuronic acid (Heiander et al., 1995). However, in people, 5-HTOL is typically the minor serotonin metabolite; its concentration is typically less than 1% of 5-HIAA. It should be mentioned that only a tiny portion of the serotonin metabolites expelled in urine come from CNS sources; the majority come from peripheral sources (Aizenstein and Korf (1979); Some and Helander, 2002, reported that the higher level of 5-HIAA was found in hamster urine (89.3 μmol/L) and (85.2 μmol/L) in mouse urine, and the small possible in horse, sheep, and rainbow trout (range 2.0–3.7 Amol/L). Generally in human, 5-HIAA range in urine ~5–40 μmol/L (Some and Helander, 2002). The urine 5-HIAA/5HTOL ratio, an easily available indication of the relative importance of the oxidative and reductive routes for serotonin metabolism, was found to differ significantly between species in this study.

2.3.3. Levels of serotonin in tear

Human tears include serotonin, a neurotransmitter made of nociceptor sensitization (Szewczyk et al., 2023). Over the world, millions of men and women suffer from dry eye (DE), a multifactorial condition affecting the ocular surface and tear film (Rathnakumar et al., 2018). Serotonin levels in tears correlate as a nociceptor sensitization marker to aspects of DE, such as signs and symptoms. Chhadva et al., 2015

reported that the tear fluid of serotonin levels in the "dry eye" can be analyzed as symptomatic aqueous-deficient with higher serotonin levels and symptomatic but with average tear-producing with less serotonin levels (Chhadva et al., 2015). In animal studies, irritation has been demonstrated to either directly or indirectly impact peripheral nerve function by upregulating the production of serotonin, its receptors, and other neuropeptides that sensitize peripheral nerves (Cardenas et al., 1999). However, sufficient research evidence supports that serotonin, the peripheral nerve sensitizer, acts through primary signals' over-produced receptors for serotonin, which leads to peripheral sensitization and an increase in pain signals. An ELISA was used to measure the 0.30 ng/mL level of serotonin in tears (serotonin ELIS kit) (Enzo Life Sciences, Inc. Farmingdale, NY, USA) (Chhadva et al., 2015). Martine et al. research study has reported serotonin levels in tears starting from 0.12 ng/ml to 50.32 ng/ml with an average range of 2.74 ng/ml respectively (Martin, X. and Brennan, M., 1994a, 1994b). Finding a trustworthy, point-of-care diagnostic test is the next step to quickly and accurately quantify serotonin from tear fluid of essential molecular components related to DE pathobiology.

2.3.4. Levels of serotonin in saliva

Human saliva contains serotonin, a catecholamine that is crucial for mood regulation. Numerous hormones, steroids, peptides, and amines are found in human saliva. To shed light on this, scientists have found correlations across psychological markers like self-reported stress biomarkers and salivary hormone levels like cortisol and cytokines (Karuppaiah et al., 2023). Salivary serotonin may be derived from the blood since it is yet unknown if the serotonergic pathway projects directly from the brain to the salivary glands (Ferreira and Hoffman, 2013; Matsunaga et al., 2017). Serotonin is also identifiable in human saliva with a standard range of 0.18–5.5 nM (Adumitrăchioaie et al., 2019). The serotonin detection technique in human saliva often involves developed strategies due to its lower concentration, high cost, and time-consuming process. It is driven by the increasing requirement for fast-in-situ analytical procedures in various applications. The diurnal regularity of salivary serotonin secretion in major depressive disorder patients was examined in a previous study. Fluoxetine can be helpful before and after clinical treatment. This indicates that serotonin saliva might be valuable for assessing serotonergic functions (Tan et al., 2007). However, it is unknown whether salivary serotonin levels are linked to the capacity for empathy.

2.3.5. Level of serotonin in plasma

The function of plasma serotonin in the cardiovascular system includes briefly mentioning its important significance as a neurotransmitter. Platelets carry and store almost all plasma serotonin in thick

granules. Under normal physiological settings, the serotonin transporter (SERT) carries almost all of the plasma serotonin into platelets, where it is either eliminated by an MAO or sequestered in dense granules by a vesicular monoamine transporter (VMAT) (Mercado and Kilic, 2010). Mammalian platelets are the second-highest level of serotonin in the human body and contain almost all of the circulating plasma serotonin. Nevertheless, a platelet does not manufacture any of these hormones (Soslau, 2022). The serotonin plasma level is deficient in the hypertensive person, around 0.7–1 nM, and although the hypertensive person's level can rise up to 100%, the real concentration only varies by 0.35^{-1} nM (Brenner et al., 2007). According to several pieces of research, systemic hypertension is directly correlated with plasma serotonin, vasoconstrictive activity (Yildiz et al., 1998), and antagonists lower blood pressure (Woittiez et al., 1985). In patients with uncontrolled hypertension, the salient indication of excess serotonin is supposed to be carcinoid syndrome and serotonin syndrome (Jafri et al., 1992). Furthermore, patients with type 1 and type 2 diabetes have lower plasma serotonin levels, which may be related to decreased insulin action and ultimately impact serotonergic neurons in the brain that are linked to neuropsychiatric disorders (Fraer and Kilic, 2015). Other investigations observed that higher plasma serotonin amounts in mice changed the content of N-glycan of platelet surface glycoprotein, which was assumed to increase the aggregation of platelets. Further research has revealed that transglutaminases, which change the response of platelets, can irreversibly attach serotonin to proteins (serotonylation) (Bader, 2019). Numerous cell types and organs appear to be affected by this relatively new field of inquiry, and many questions remain.

2.3.6. Level of serotonin in blood

One of the most important biological fluids is the entire bloodstream, which offers vital information for medical diagnosis and illness treatment. In the past ten years, developments in diagnostic research, microfluidics, and nanobiotechnology have expedited the development of dependable, small-sized diagnostic equipment for whole-blood testing with the eventual objective of disease surveillance (Doldán et al., 2016). To regulate intestinal motility, the enterochromaffin cells of the GI tract produce nearly most of the serotonin. Although platelets do not produce serotonin, it is incorporated and stored by abdominal enterochromaffin cells and released into the bloodstream (Duerschmied et al., 2013). Platelets in the bloodstream widely play an essential role in prime hemostasis, which means stopping bleeding following a ruptured blood vessel (Ge et al., 2009). Dense platelet granules release serotonin during platelet activation, primarily responsible for platelet aggregation and vasoconstriction of the surrounding blood arteries, which aid in hemostasis (Berger et al., 2009a). The inner membrane of platelets contains several specific subcellular compartments, such as adhesive, proteins in α -granules, and ions in dense-body granules. When platelets come into contact with collagen during vascular rupture, they start a series of biological reactions that end with the release of materials from both dense-body and α -granules (Ge et al., 2009). Selective serotonin reuptake inhibitors (SSRIs) are the first line of treatment for primary hemostasis. By preventing platelet serotonin from being taken in and stored, SSRIs may increase the length of bleeding, especially in patients who are already taking anticoagulants or are at high risk of bleeding. Platelets carry serotonin to various tissues and serve as the primary source of serotonin for lymphatic arteries and immune cells that express MOA (Rodríguez et al., 2001). Lymph tissue primarily obtains its serotonin from the blood, while mast cells, monocytes, and T cells can also seem to produce trace amounts of serotonin (Baganz and Blakely, 2013). Serotonin levels in the blood range from 0.4 μ M to 2.6 μ M on average in healthy youngsters and between 0.6 and 1.6 μ M on average in adults (Peaston and Weinkove, 2004). Serotonin imbalances have been linked to severe conditions such as bipolar illness, anxiety, autism, and inflammatory diseases (Li, S. et al., 2023b).

3. Electrochemical biosensors for serotonin

Over the past several decades, electrochemical sensors have been the most extensively utilized technology to detect serotonin molecules owing to their straightforward instrument operation, quick responses, high sensitivity and resolution, linear output, low power consumption, low cost, high repeatability, and accuracy. Three issues hold back evaluating serotonin role within the primary serotonergic network. (i) Serotonin release is comparatively low to other neurotransmitters outside the cell. (ii) Diverse types of receptors for serotonin and downstream activities cause serotonin transmission at radically diverse time scales. (iii) Serotonin is found in serotonergic neurons in the brain and has a molecular structure similar to other monoamine neurotransmitters, including histamine, nor-epinephrine, epinephrine, and dopamine, among the most firmly established devices for serotonin recognition in biological materials. Understanding the entire function of serotonin in vivo procedures demands precise measurements with high sensitivity and spatiotemporal precision. Studying serotonin homeostasis is crucial for the scientific research of the nervous system as well as for the creation of new, quick, cheap, and more potent treatments for neurological conditions like anxiety, depression, and mood swings. An electrochemical biosensor can monitor either biological or non-biological matrices can be divided into four primary categories: impedimetric biosensors, voltammetric/amprometric, conductometric, and potentiometric Biosensor,

Impedimetric Biosensors: The capacitive and resistive characteristics of materials are measured using electrical impedance spectroscopy (EIS) when the system is perturbed by a small amplitude sinusoidal AC excitation pulse (approximately 2–10 mV).

Amprometric/Voltammetric Biosensors: Biosensors that use amprometric or voltage meters measure current by adjusting the voltage applied to a working electrode (WE) concerning a reference electrode. The limit of the current arising from electrolysis, the mass transmission rate of the particles that respond to the entire solution to the electrode interfaces, is now known as electrical oxidation or reduction at the WE. By monitoring the current applied at a constant voltage at the WE surface when the reference electrode is present, amprometry biosensors enable the detection of a target analyte. When the potential is raised at a specific pace using voltammetric biosensors, the current response typically peaks or plateaus concerning the concentration of the target analyte.

Conductometric Biosensors: Conductometric biosensors monitor changes in the electrochemical conductivity of a mixture as its constituent parts change during a chemical reaction. Enzymes that produce charged products that alter the ionic strength of the sample mixture and increase solution conductivity are frequently found in conductometric biosensors (Ronkainen et al., 2010). In general, capacitive biosensors provide more insight into the insulating qualities of capacitance measurements. Generally speaking, even slight desorption on the sensing surface increases the baseline (Labib et al., 2009).

Potentiometric Biosensors: Potentiometric biosensors can estimate an electrochemical cell's potential (V) while representing negligible current. These chemical biosensors mainly use a charged ion of interest that interacts with an ion-selective membrane in an electrochemical cell with two reference electrodes that effectively measure its voltage. Potentiometric measurements Biosensors coated with biological components, including enzymes, frequently catalyze the process, forming ions that the bare-designed electrode can detect (Ronkainen et al., 2010). All the above voltammetric approaches are the most broadly established in electrochemical biosensing. The measurement technique mentioned above is the most flexible and straightforward in generating and interpreting signals. Several stable compounds use β -cyclodextrin as a recognition element in electrochemical biosensing platforms for serotonin. A composite of β -cyclodextrin, N-acetylcholine, and MWCNTs was added to a carbon electrode for electrochemical serotonin biosensing. The amprometry sensing technique used for the serotonin

concentration range was shown to be linear from 2 to 200 μM , with an RSD of less than 5% and a limit of detection (LOD) that reached the sub-micromolar level (Abbaspour and Noori, 2011).

The application of particular serotonin molecules has also been investigated, such as in an electrochemical sensor that uses a self-assembled monolayer of captopril and thiophenol combined on the Au-electrode surface (Mozaffari et al., 2010). Serotonin molecules were selectively trapped by forming a solid, increasing the charge-transfer barrier to a redox probe, forming a compound with the monolayer, or providing an anodic uncovering current during an anodic scan due to the complex's blocking action. Serotonin was detected with a dynamic range of two or three orders of magnitude and a LOD of 28 and 1.2 nM, respectively, using differential pulse anodic stripping voltammetry (DPASV) and EIS. Electrochemical measurement is employed in the real-time evaluation of serotonin in bio-samples using a carbon fiber microelectrode to monitor serotonin released from platelet granules (Ge et al., 2011). Notably, the electrode's superior sensitivity, increased temporal precision, and capacity to produce a cyclic voltammogram signature for serotonin identification led to its selection. With a LOD of 0.36 nmol/ 10^7 platelets, the biosensor enabled sensitive serotonin detection using fast-scan cyclic voltammetry (FSCV).

An electrochemical sensing portable instantaneous neurotransmitters level was created to facilitate FSCV at the level of a carbon fiber microelectrode for actual time serotonin quantification (Griessenauer et al., 2010). FSCV optimization for the serotonin detection consisted of the N-waveform being scanned linearly from +0.2 to +0.1 V and then from -0.1 V to +0.2 V at a rate of 1000 Vs⁻¹. High accuracy electrically provoked the production of serotonin in the dorsal raphe nucleus of mice brain slices and flow cell injection analysis. Such biosensors exhibited an LOD of 10 μM in the dorsal raphe nucleus of rat brain slices. Recently, Holmes et al. reported glutamate-electropolymerized against carbon fiber microelectrodes (CFMs) and facilitated responses for serotonin and dopamine in vivo improved sensitivity of single-electrode FSCV at lower concentrations (Holmes et al., 2021). This study's original goal was to improve the sensitivity of FSCV toward serotonin in vivo conditions where a 2-fold sensitivity increase was achieved.

3.1. Surface modification of electrode-based serotonin biosensor

Carbon modification electrodes with different chemical and biologically active compounds are broadly used in biosensing platforms. Their good electron transfer kinetics, low cost, good chemical inertness, broad potential window, low current background, biocompatibility, and stability make them appropriate sensing properties. However, GCE is the most common electrode for electrochemical biosensing serotonin because of its exceptional conductivity in electricity, superior mechanical and biochemical stability, gas resistance, and enormous potential window. A well-defined serotonin oxidation peak is broadly displayed at 400 mV at bare GC-electrodes (Goyal et al., 2008). In 1998, Zen et al. reported the first surface-modified GC electrode that detected serotonin (Zen et al., 1998). SWV was used to modify the GC electrode using Nafion and a ruthenium oxide pyrochlore catalyst (Nafion/RuO₂ pyrochlore/GCE). Nafion is a polyelectrolyte that exchanges cations only-anions cannot move and is a sulfonated tetrafluoroethylene molecule. Ruthenium-oxide pyrochlore catalysts have significant advantages achieved by composition for the electrocatalytic function, Nafion charge restriction, and preconcentration characteristics. This chemically modified electrode showed a LOD of 2 nM, linearly ranging from 0.01 $\pm$ 0.5 mM to 2 $\pm$ 20 mM.

Furthermore, the electro-polymerization of polymeric compounds on the bare electrode surface offers a consistent layer of coating materials (Chavan et al., 2022a). The electropolymerized poly(phenosafranine) film coating on the oxidation peaks towards serotonin and other neurotransmitters (dopamine and ascorbic acid) was separated when the GCE was barren. It was discovered that the serotonin detection limit was 20 nM (Selvaraju and Ramaraj, 2003). Serotonin is one of the critical

electrically measurable neurotransmitters and metabolites, which are tryptophan derivatives. During biosynthesis, tryptophan hydroxylase transforms tryptophan to 5-hydroxytryptophan, which is subsequently decarboxylated to create serotonin. The metabolic breakdown of serotonin is mainly caused by monoamine oxidase, succeeded by an aldehyde dehydrogenase enzyme that accelerates 5-hydroxy indole acetic acid. The conversion of serotonin to 5-hydroxytryptophan is a minor process. Additionally capable of oxidizing, tryptophan derivatives have similar peak potentials at physiological pH and can be electrochemically monitored in two-electron oxidation processes. Multiple distinct secondary reactions have been reported following oxidation. The intricate chemical pathway entails the dimerization of serotonin and the creation of tryptamine-4-5-dione upon the addition of water. Electrochemically active properties of serotonin can be directly determined by the electrical oxidation of the molecule on the electrode surface (Robinson et al., 2008). However, electrochemical detection of serotonin is usually complicated by the additional electroactive molecules in bio-samples like dopamine, which interferes with the serotonin signal, whereas serotonin oxidation potential closes to dopamine. Additional interfering biomolecules such as ascorbic and uric acid need higher levels and parallel oxidation potentials to serotonin at conventional bare electrodes (Kim et al., 2012; Robinson et al., 2008). Electrochemical determination offers the benefits of extreme sensitivity, good stability, comprehensive linearity, and lower prices associated with electrical evaluation. Additionally, the serotonin oxidation products reduce the electrode's reusability and reproducibility, absorbed on the bare electrode surface. Recently, in 2020, Lee et al. reported that a 25 μm Pt-ultramicroelectrode (UME) was utilized in cyclic voltammetry (CV) to determine the oxidation potential of serotonin in a single human platelet Fig. 4a (Lee et al., 2020). The ultramicroelectrode was submerged in a solution containing the human platelets to be identified to measure the current-time (i-t) curve. Serotonin in the platelet oxidizes when it collides with the electrode, and the electrochemical reaction generates an anodic peak current and quickly calculates the serotonin concentration distribution in the single platelets. The average diameter assuming single platelets is 3 μm and spherical shape. In the single-entry electrochemical method, a specific platelet serotonin level of 178 μM was measured using an integrated charge value of approximately 486 fC. In this practice, considering the clinical importance of serotonin, this approach can clearly measure serotonin levels from each platelet.

Yola M. et al. reported that serotonin could be detected in urine samples using 2-D hexagonal boron nitride (2D-hBN) changed by placing a molecularly imprinted polymer atop GCE and a graphene quantum dots nanosheet on it (Yola and Atar, 2018) (Fig. 4b). The linearity range of this electrochemical biosensing serotonin was determined to be 1.0×10^{-12} to 1.0×10^{-8} M level, with a LOD of 2.0×10^{-13} M. The resultant electrodes were appropriate for immediately detecting serotonin in urine samples and showed remarkable selectivity to this neurotransmitter over dopamine, tryptophan, and norepinephrine because of the molecular imprinting polymer's strong binding affinity to serotonin. Because graphene and its derivatives have strong electrical, electrochemical, and biocompatibility benefits, many reports have used them as electrochemical sensors for sensitive component diagnostics (Nair et al., 2022). Recently, Liu et al. reported that flexible B- and N-codoped vertical graphene electrodes for serotonin detection in body fluids were created by growing boron (B-) and nitrogen (N-) co-doped nanosheets of graphene vertically on flexible tantalum (Ta) strip substrate (Liu et al., 2023) (Fig. 4c). This (B-) and (N-) based sensor studies displayed a quantitative reactivity towards serotonin linear range from 0.10 to 224.43 μM , which depends on the pH range of 1.5–9.0, alongside the serotonin detection limits exhibited 0.009–0.266 μM (S/N = 3). The figure shows a schematic of a developed biosensor diagnosis of serotonin in intestinal juice, stomach fluid, and blood samples that are more stable and sensitive. The efficient sensing platform for detecting serotonin, a brain chemical, is designed to effectively flexible (B-) and (N-) bio-interface. This can help design and fabricate

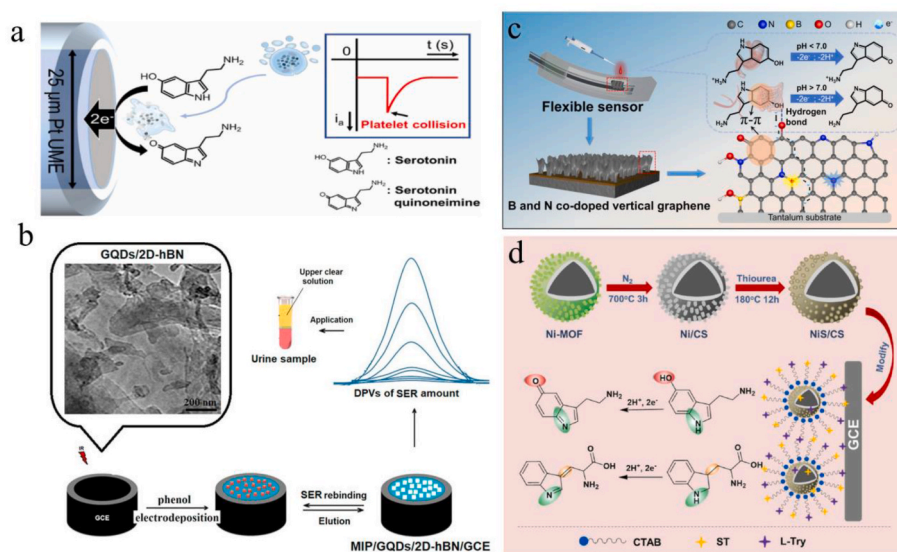


Fig. 4. a) Diagrammatic representation of serotonin oxidation in a single platelet Via SEE method. The peak current is seen when a platelet and a UME clash because the platelet's serotonin oxidizes on the electrode. (Lee et al., 2020). Copyright © 2020, American Chemical Society. b) The schematic procedure of molecular imprinting polymer of GQDs/2D-hBN/GCE (Yola and Atar, 2018). Copyright©2018 Elsevier. c) Schematic showing the production of the B-N co-doped vertical graphene (BNVG) sensor, the mechanism of the serotonin response, and the detection of body fluids (Liu et al., 2023) Copyright©2023 Elsevier. d) The construction of 3D NiS/CS hollow microspheres (Dong and Zhang, 2022). Copyright©2022 Published by Elsevier.

neurological devices and medical-care products.

Additionally, Dong et al. reported on NiS/carbon hybrids, which are utilized to create catalysts for electricity for the simultaneous electro-oxidation of L-tryptophan and serotonin. NiS particles are inserted into three-dimensional hollow-porous carbon microspheres (NiS/CS) through consecutive carbonization and sulfidation Ni-MOF (Dong and Zhang, 2022) (Fig. 4d). The present work used the self-templating technique employing Ni-MOF as a precursor and a series of carbonization and sulfidation steps to create 3D NiS/CS hollow microsphere. Notably, the CTAB/NiS/CS GC-electrode was created by the combined amplification of the hydrophobic characteristics of surfactant CTAB connection and the increased electrocatalytic performance. For serotonin and L-tryptophan, the sensor that was developed yielded a linear scale of 0.01–200.0 μmol/L with an LOD of 3.35 and 2.94 nmol/L, respectively. This study created a new method for serotonin electrochemical sensing, which may be helpful in the biomedical area. It also shows a higher sensitivity to serotonin and L-tryptophan, protecting successfully from other simultaneous interference.

3.2. Nanomaterials-based serotonin biosensor

3.2.1. Carbon nanotubes (CNT)

During the last 20 years, biosensors based on nanomaterials have vastly improved (Schroeder et al., 2019). Graphene, CNTs, and graphene with quantum dots are examples of carbon-based nanomaterials that have generated much attention in scientific research due to their extraordinary mechanical, electrical, and photophysical capabilities (Hong et al., 2015; Xu and Zhao, 2023). It has demonstrated applications across biosensing, imaging, drug delivery, advanced materials, micro-electronics, and others (De Volder et al., 2013). Multi-layered tubes known as multi-walled carbon nanotubes (MWCNT) and single-walled carbon nanotubes (SWCNT), a single rolled-up cylinder of graphene, are the precursors of CNT. SWCNTs are especially fascinating due to their sensitivity to the environment and optoelectronic characteristics, making them specific and appropriate biosensing (Chen et al., 2006). SWCNT is frequently used to identify the chiral index (n, m), where n then m represent the lattice structure of carbons shown in Fig. 5a. The properties of SWCNT are dedicated based on the exact sp^2 -hybridized carbon lattice and the number of rollup cylinders that are

arranged into a stack of each other (Dresselhaus et al., 2004; Iijima and Ichihashi, 1993). Principally, the SWCNT is a rolled-up vector $c = na_1 + ma_2$ (a_1 and a_2), which are the graphene lattice vectors. Therefore, SWCNTs' roll-up vector diameter was determined to be from 0.4 nm to 10 nm and have a length of several cm shown in Fig. 5b (Dresselhaus et al., 1998). The SWCNT rolled-up vector affects the density and energy of the optoelectronic state, which are directly related to chirality. The results responses of n and m value SWCNTs can exhibit metallic ($n - m = 0$), semi-metallic ($n - m = 3x$ ($x \in \mathbb{N}/(0)$) or semiconductive properties (remaining (n, m), chirality's) (Kruus et al., 2013). During the SWCNT lifetime, excitation of the electron pair can be made and diffused alongside the SWCNT axis. To understand the electronic and photophysical relationship of semiconducting SWCNT, they have grown in the near-infrared spectrum (NIR, 800–1700 nm) because of their electronic gap band. The optoelectronic state density of the nanotubes semiconducting carbon as shown in Fig. 5c. The semiconducting SWCNTs, photon energy absorption in the visible light spectrum usually results in stimulation of the next conducting band.

Considering the importance of endogenous gastrointestinal neurotransmitters, the specific detection of serotonin has also attracted passionate attention in medicinal and life science studies. Ghazala et al., 2021, reported a basic two-step electrochemical procedure for clinically relevant serotonin levels in biological serum and urine samples. A transitory amount of Pt-NPs (platinum nanoparticles) has been subsequently deposited onto the CNT core incorporating Cu₂O metal oxide (MO) (Ashraf et al., 2021) (Fig. 5d). To evaluate electrocatalytic studies of modified CNTs-Cu₂O-CuO@Pt/GCE in the presence of serotonin, CV records have been performed. The oxidative signal response is fast and eastward, reaching an LOD of 3 nM in 4 s. It has remarkable durability, reliability, and a consistent 95% current response with a linearity from 15 nM to 3 mM. Sun et al. recently predicted the simultaneous identification of serotonin along with additional neurotransmitters using an electrochemical CNT-based nano-biosensor. After CNTs were introduced to GCE, poly(3,4-ethylene dioxathiophene) (PEDOT) and nickel(II) oxide (NiO) were incorporated (Fig. 5e). When CNTs were present, serotonin and dopamine could be distinguished from one another. In order to produce this sensor, CNTs and PEDOT were added to an aqueous solution of KCl and NiCl. Ni/CNT/PEDOT was then electrochemically deposited on a GCE template with the help of CV. Moreover, the nano

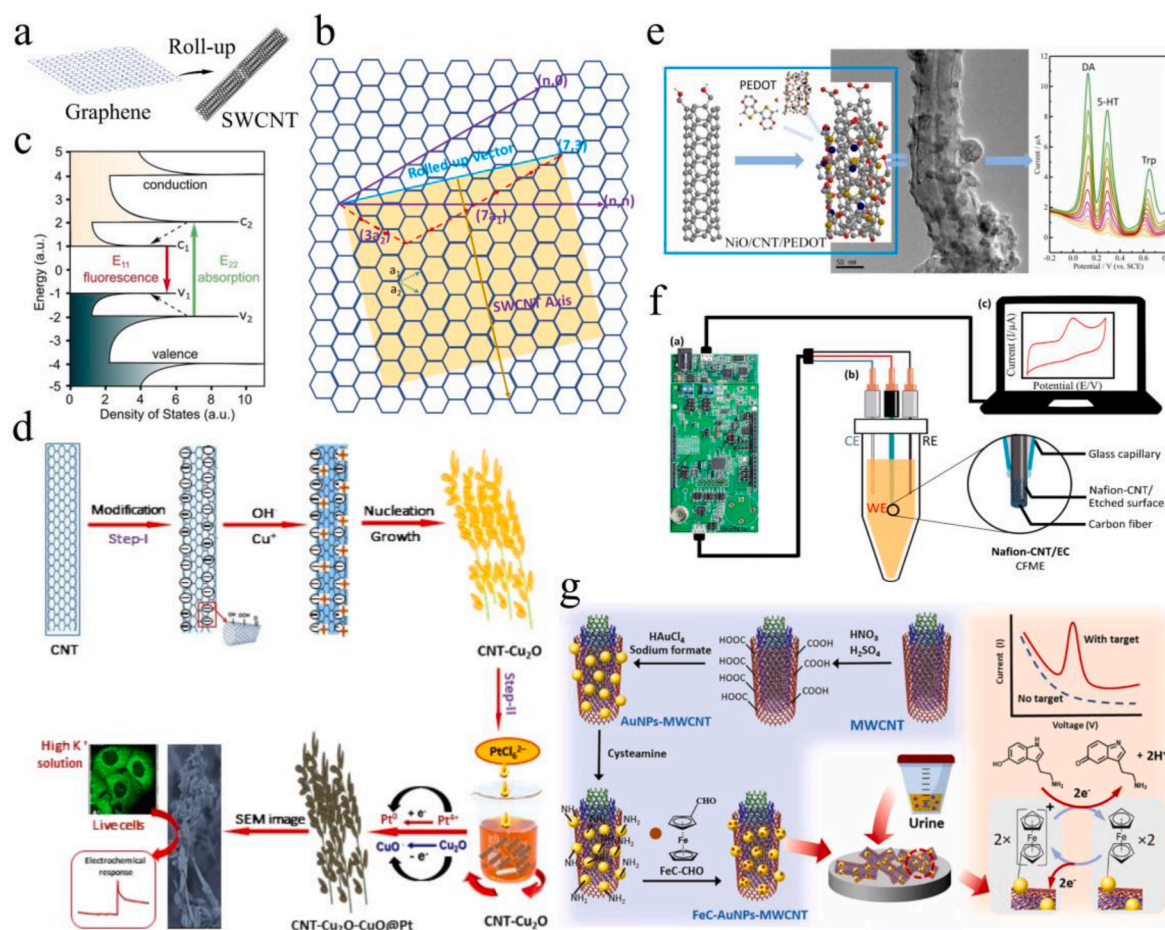


Fig. 5. a) A sheet of graphite monolayer can be rolled up to explain the graphical representation of SWCNTs. b) The framework that produces SWCNTs involves superimposing the first and last carbon atoms and rolling up the graphene sheet according to the roll-up vector. Parallel to the roll-up vector is the tube axis. c) The bandgap architecture of near-infrared (NIR) fluorescence emission. d) Schematic presentation of fabrication flow of the CNTs-Cu₂O-CuO@Pt heterogeneous structures. It is reprinted with the reference approval (Ashraf et al., 2021). Copyright © 2021, American Chemical Society. e) Schematic drawing of NiO/CNT/PEDOT composite formation mechanism on the GC electrode. Reprint permission has been obtained from ref (Sun et al., 2018). Copyright © 2017 Elsevier. f) Diagrammatic representation of the portable serotonin diagnosis system based on Nafion-CNT/EC CFME: (a) the IC, (b) the biosensing component, and (c) the PC with a software interface (Han et al., 2023). It is reprinted with the reference approval. Copyright © 2023 Royal Society of Chemistry (RSC). g) Schematic of FeC-Gold-NPS-MWCNT nanocomposite synthesis. The mechanism of serotonin sensing. The image of a sensor is seen in the inset (Wu et al., 2022). Copyright © 2021 Elsevier.

biosensors structure included PEDOT and NiO to increase its sensitivity to biological chemicals. According to the experimental data, serotonin has a linear domain of 0.3–35 μM and a LOD of 0.063. Furthermore, after thirty-seven days, the nano biosensor maintained 95.3% of its signal for recognizing serotonin (Sun et al., 2018).

In order to diagnose serotonin in fake urine samples, Han et al. reported on the electromechanical modification of carbon fiber micro-electrodes (Nafion-CNT/EC-CFMEs) and the combination of Nafion and CNTs (Han et al., 2023) Fig. 5f. The present investigation involved the dip-coating of Nafion-CNT film onto the small carbon fiber electrodes, followed by an increasing the electrode surface area and enhancing serotonin sensitivity with electrochemical therapy. The proposed sensitivity of the portable serotonin biosensing device was determined to be 0.074 $\mu\text{A } \mu\text{M}^{-1}$ and its LOD was 140 nM. This technique demonstrated almost full recovery rates when used to test spiked serotonin in fake urine samples. The suggested portable serotonin diagnosis device offers straightforward and adaptable point-of-care testing in the form of sensitive electrochemical readings. The electrochemical portable sensing system will eventually be enhanced as a wearable or implanted device to enable ongoing tracking of serotonin levels in people or animals. It will also be further reduced in size to create a smaller footprint.

3.2.2. Multiwall carbon nanotubes (MWCNTs) based serotonin sensor

In the last two decades, MWCNTs have emerged as an important industrial material. Iijima studied the morphological structure of MWCNTs with an electron diffraction and high-resolution transmission electron microscope (HR-TEM) (Iijima, 1991). MWCNTs are valued at about \$631.5 million in production value worldwide. MWCNTs are mostly used in catalysis because they are inexpensive and widely available. MWCNT (5–10 walls) has a surface area and porosity of about 200–300 m^2/g Peigney et al. (2001); After Iijima's 1991 report on CNTs, the system of CNT was thoroughly investigated and synthesis by chemical vapor deposition (CVD) in a 2-h procedure, exposing 1 g of oxide catalyst in combination with spinel-type cobalt-manganese to an ethylene/hydrogen feeds at 650 °C can yield around 180 g of MWCNTs (Tessonier et al., 2010). As studied globally, the MWCNT is the primary type of carbon nanomaterial for catalytic application, and it commercializes over 95% of nanocarbon production (Su et al., 2013). A wide range of possibilities in nano-biosensors is made possible by the unique qualities of MWCNT, which include larger conductivity of electricity, higher modulus and elasticity, reactivity, uniform structure, and functional properties at the nanoscale level. In particular, the electrodes exceptional chemical stability, electrical conductivity, and biocompatibility were shown when applied as a surface modification.

However, Kangbing et al. Reported the determination of positively

charged neuro-molecule serotonin is actively adsorbed on the MWCNT modified graphite electrode of porous interfacial surface selectively discriminated anodic peak of serotonin and other neuromolecules (dopamine and ascorbic acid) provides higher sensitivity (Wang et al., 2003). The CNT-modified electrode enabled significantly improved LOD, was capable of an antibacterial agent with oxidizing substances, and showed lower current than GC and boron-doped polycrystalline diamond electrodes. Likewise, MWCNTs compacted polymer electrodes made of composites can be used to improve electrochemical efficiency (Fagan-Murphy and Patel, 2014). In 2011, Kim et al. developed a poly (meso-tetrakis-(2-aminophenyl) porphyrin)-SWCNT-modified GCE for serotonin identification that had a LOD 10^{-3} μM and permitted the existence of dopamine and ascorbic acid (Kim et al., 2011). Mazloum et al. presented MWCNTs functionalized with benzofuran derivative on GC electrodes followed by CNTs modified with TiO_2 nanoparticles and ionic liquid (IL-DC-CNT/GC) with benzofuran derivative (DDF-CNT- TiO_2 /IL/GC) (Mazloum-Ardakani and Khoshroo, 2014). These studies considerably enhanced the oxidation currents of serotonin, negatively shifted oxidation potentials, and resolved the overlapped serotonin peaks of anodic, isoproterenol, and norepinephrine, respectively. Goyal et al. reported a promising and susceptible serotonin electrochemical sensor using silver (Ag) irradiated MWCNTs (Goyal and Agrawal, 2012). This study exposed MWCNT to high-energy Ag ions (~ 120 MeV) at various fluences ($1\text{e}12$, $3\text{e}12$, and $1\text{e}13$ ions cm^{-2}). The irradiation sensor successfully measured serotonin and adrenaline in a variety of human urine samples once the experimental settings were optimized. As peak overlapping resulted in increased sensitivity and detection limits 2 nM and 0.75 nM with a range of 0.1–105 μM from the biological fluids for both neurotransmitters, irradiation reproducibility remains challenging. In another investigation, a simple electrodeposition of MWCNT/polypyrene(PPy)/Ag-NPs nanohybrid has been constructed on Pt-electrodes to recognize serotonin in plasmatic serum. Higher electroactive surface area owing to synergistic effects and a lower LOD for serotonin has been achieved, resulting in higher anodic current strength (Cesarino et al., 2014). An outstanding electrocatalytic capability in the electro-sensing of serotonin-based on MWCNTs treated with zinc, nickel, and iron-oxide nanoparticles composite was also produced by the interaction between MWCNTs and metal-oxide nanoparticles, where the MWCNT-NiO-modified GC-electrode demonstrated more excellent identifying properties compared to other metal oxide nanoparticles (Fayemi et al., 2017).

In recent approaches, Wu et al., (2022) informed a selective and sensitive electrochemical bio-sensor employing electrocatalytic nanocomposites and ferrocene (FC) particles covalently bonded AuNPs on MWCNT to improve serotonin detection (Wu et al., 2022). The nanocomposite selectively deposited on the screen-printed electrode takes the benefit of improved enzymatic characteristics of the FeC particles and Au-particles with high density, and the conductivity of the carbon nanotube exhibited a sympathetic electrical reaction to serotonin oxidation Fig. 5g. During an FC electrically oxidized to produce ferrocenium ions (FC^+) during anodic scanning (Nickolson and Shain's model can be used to explain ferrocyanide-catalyzed serotonin oxidation) (Nicholson and Shain, 1965). As illustrated in the schematic of three modified screen-printed electrodes, MWCNTs modification increased current significantly because the higher density network expanded the electroactive surface area. The developed FC-AuNPs-MWCNT changed the SPC-electrode and performed 61 times more electrocatalytic activity for serotonin oxidation than the original SPC-electrode. The suggested sensor demonstrated enhanced sensitivity with a broad dynamic limit of 0.05 μM –20 μM , an estimated LOD of 17 nM ($\text{S/N} = 3$), outstanding repeatability, and elevated serotonin selectivity against several neurotransmitters. The majority of the biological fluid's physiological serotonin concentration range was covered by this detection range. due to the compound catalyst's strong catalytic activity, FC-decorated AuNPs, and the MWCNT networks better electrical conductivity.

3.2.3. $\text{Ti}_3\text{C}_2\text{T}_x$ MXenes-based serotonin biosensing

This section discusses the electrochemical properties of $\text{Ti}_3\text{C}_2\text{T}_x$ -MXenes in developing electrochemical biosensors for detecting serotonin neuromolecules. $\text{Ti}_3\text{C}_2\text{T}_x$ -MXenes depend entirely on their surface chemistry, structure, composition, and interlayer spacing (VahidMohammadi et al., 2021). The fundamental formula for MXenes, a family of two-dimensional (2D) transition metal carbide compounds produced by selectively etching the A layer from the parent MAX phase, is as follows: $\text{M}^{n+1}\text{AX}_n$ is the phase where M stands for transition metals (such as Ta, V, Cr, Ti, Nb, and Mo), A is the element of the group that is mostly $1/3$ A or $1/3$ A, X is C and N, and n is the integrated value between 1 and 3. Transition metals (such as Ta, V, Ti, Nb, Cr, and Mo) are represented by M. The O, F, and OH functional groups are often present on the exfoliated surfaces of $\text{Ti}_3\text{C}_2\text{T}_x$ -MXenes that are added during the chemical etching process (Tang et al., 2012). The surface chemistry of $\text{Ti}_3\text{C}_2\text{T}_x$ -MXenes is electronically tunable, and the selection of synthetic methods significantly influences the proportion of these functional groups on the surface of the MXene synthesis. The monolayers of $\text{Ti}_3\text{C}_2\text{T}_x$ -MXenes are estimated to be metallic and have a higher density of electrons close to the Fermi level (Hart et al., 2019; Xie and Kent, 2013). The metallic properties of MXenes as an electrode material have predicted a controllable function between 1.6 and 8.0 eV and a high conductivity of $\sim 10^4$ S/cm (Jeon et al., 2020). The form and amount of these interface resignations significantly impact the properties of MXenes, as demonstrated by the use of density functional theory (DFT) computation. This allows for the analytical achievement of $\text{Ti}_3\text{C}_2\text{T}_x$ -MXenes to be tailored to various purposes (Junkaew and Arroyave, 2018). Recent surveys have shown that the availability of surface chemical groups (F, OH, and O) and their metallic and adjustable conductivity make $\text{Ti}_3\text{C}_2\text{T}_x$ -MXenes a new class of exciting materials for electrochemical biosensing applications (Amara et al., 2023). However, target-specific bio-receptors, such as DNA/RNA, aptamers, nucleic acids, enzymes, and proteins, are used in electrochemical biosensors to identify the targeted molecule (Mohammadniaei et al., 2019). It is possible to design the MXene-based electrochemical biosensor by immobilizing the specific bio-receptor interaction with target molecules on the sensing interfaces to produce an electrochemical signal of greater magnitude (Chavan et al., 2024; Koyappayil et al., 2022). This electrochemical sensing platform MXene is a 2D material whose layered structure resembles an accordion (Zhang et al., 2019), has outstanding conductivity for electricity (2400 S/cm) (Wang et al., 2019), larger area surface (98 m^2/g), excellent hydrophilicity, elemental permanence (Koyappayil et al., 2020), and advantages in detection limits. These kinds of sensors can be applied in intricate biological settings with various chemical interference and can detect minuscule analyte concentrations. Recently, in 2023, Yang et al. systematically summarized MXene-based electrochemical biosensors for the detection of different neurotransmitters (dopamine, serotonin, epinephrine, norepinephrine), and also discussed the challenges and opportunities that currently exist for these biogenic amines (amino acids (Tyr), soluble gases (NO), and H_2S) (Yang et al., 2023). However, Chen et al. report utilized $\text{Ti}_3\text{C}_2\text{T}_x$ -MXene and loaded on the surface using a triangular silver nanoplate ended with L-cysteine modeling an electrical sensor (Tri-AgNP/L-Cys/MXene), for identification of serotonin (Chen et al., 2021) (Fig. 6a). The electrocatalytic serotonin oxidation two-proton–two-electron process by Tri-AgNP/TSC, Tri-AgNP/L-Cys, and Tri-AgNP/L-Cys and for the serotonin electrocatalytic oxidation, MXene offers more active sites with a range of linearity 0.5–150 μM and a minimum LOD of 0.08 μM . This biosensor has shown good recoveries, and the range of 95.38–102.3% in serum samples, and the RSD range was calculated at 2.2–3.4%.

Very recently, Su et al. prepared $\text{Ti}_3\text{C}_2\text{T}_x$ -compact nanocomposite of oxide graphene ($\text{Ti}_3\text{C}_2\text{T}_x$ -rGO) modified on the GCE to the identification of serotonin from human biofluids (Su et al., 2022) (Fig. 6b). The $\text{Ti}_3\text{C}_2\text{T}_x$ -rGO/GCE demonstrated exceptional electrocatalytic efficiency for oxidation of serotonin across a broad linear scale of 0.025–147 μM

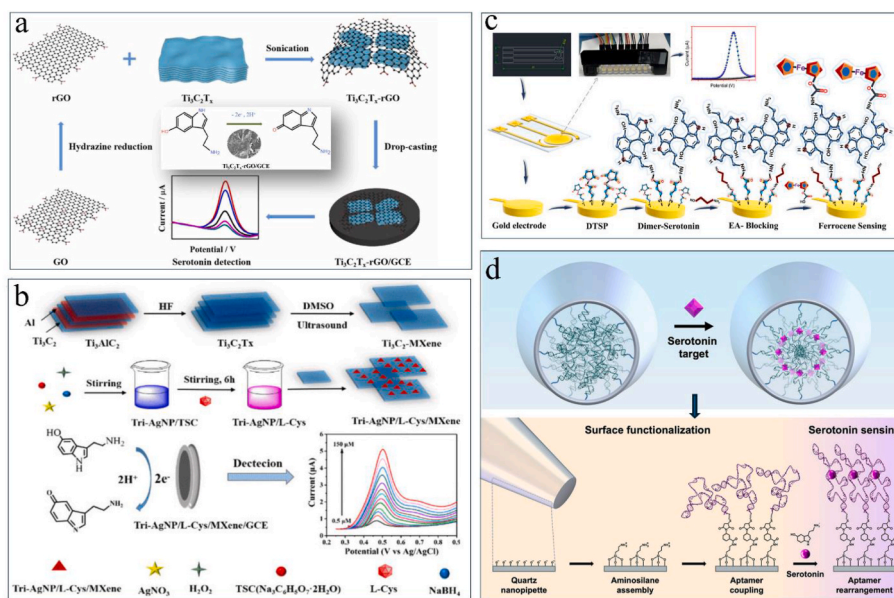


Fig. 6. Diagram showing the steps involved in creating the Ti₃C₂T_x-rGO nanocomposite and Ti₃C₂T_x-rGO/GCE (Su et al., 2022). Copyright © 2022 Elsevier. b) Schematic mechanism for Preparing Tri-AgNP/L-Cys/Ti₃C₂T_x Nanocomposites and detecting serotonin (Chen et al., 2021). Copyright © 2021, American Chemical Society c) Diagrammatic representation of the stages of modifying the screen-printed Au-surface to detect dimer-serotonin. The electro-sensor connectivity, which has 8-electrode connections in a row, was established, as shown in the top image (Chavan et al., 2022b). Copyright © 2022, American Chemical Society. d) Diagram depicting a suggested mechanism in which conformational changes in aptamers change the conductivity of nanopores after serotonin binding. Quartz nanopipettes functionalized with serotonin aptamer and a modified nanopipette sensing principle (Nakatsuka et al., 2021). Copyright © 2021, American Chemical Society.

with a minimal LOD of 10 nmol, thanks to the beneficial synergistic impact of Ti₃C₂T_x and rGO. This proposed electrochemical sensor can identify serotonin in actual plasma trials. Based on the acquired data, the predicted serotonin level in the sample was 1.5 μM. The biosensor exhibited good recovery and was between 96.4% and 107%, with the RSD less than 3.9%.

3.3. Molecular assemblies in electrochemical serotonin biosensors

Since it was brought up in the Science journal article, 'How Far Can We Push Molecular Self-Assembly,' (Service, 2005), the development of complex self-assembling systems using functional building blocks and "weak" inter and intra-molecular interactions has drawn much interest (Cao et al., 2021). Molecular self-assembly is also the only practical approach for building various nanostructures. However, ensuring the components assemble themselves correctly is not an easy task. Because the forces at work are so minuscule, self-assembling distinct molecules might get stuck in undesired conformations, making flaws impossible to prevent. Besides the necessity to identify neurotransmitters in vivo, a growing group is attempting to understand brain networks in vitro. Fortunately, existing serotonin sensing technologies have the potential to identify molecules at the single-molecule level due to their ability to restrict interactions to nanoscale volumes (Heins et al., 2005). Here, we review the first example of a molecular assembled novel electrochemical approach enzyme-mediated physiological reaction between serotonin per-oxidation to reconstruct dual-molecule 4,4'-dimeric self-assembled derivative and second electrochemical aptamer-based biosensor.

3.3.1. Dimeric serotonin based biosensing

A self-assembling 4,4'-dimer-serotonin multicomplex is created by chemically modifying serotonin through enzymatic peroxidation. It is commonly known that the peroxidase system can oxidize phenolic and indolic substances. In light of the structure of dimer-serotonin, a process of ionic was therefore postulated in the electrophilic C4' site of a transiently produced quinone imine, which was concurrently attacked by the 5-hydroxyindole nucleophilic (C4') position (Wrona and Dryhurst,

1991). In contrast to the monomeric serotonin binding sites, the dimerization structure of the phenoxy-centered radical-radical connection at the C(4')-C(4') location of serotonin provides two undistinguishable detection positions, which gives an extra opposite required connection. No other place on the serotonin residue experiences the dimeric reaction; it only happens at the C(4') position, which is situated above the indole ring of serotonin (Huether et al., 1990). Recently, Chavan et al. demonstrated an electrical biosensor based on the physiological peroxidation process between two serotonin molecules mediated by an enzyme that formed a self-assembled dimeric product (Chavan et al., 2022b) (Fig. 6c). Serotonin enhanced the enzymatic activity to form a dimerization and provided multiple binding sites that selectively interacted with two different intermolecular interactions. A DTSP linker with one terminus may have functionalized the electrochemical detecting device's gold surface, connecting to dimeric amine groups and allowing the dimeric amine groups' second edge to engage with other ferrocene signaling moieties. In the electrochemical sensing approach, such a unique concept of serotonin dimerization demonstrated high sensitivity (2.0×10^{-2} nM) and specificity immuno-sensor calculating serotonin point-of-care testing. DTSP-modified on the gold electrode sensing approach showed good linearity in dimer-serotonin from 10 to 400 nM, with a LOD of 0.9 nM in the PBS solution and 1.4 nM in the serum sample. The gold surface of the electrochemical detecting device may have been functionalized using one terminus DTSP-linker, enabling connecting to dimeric groups of amine and allowing the dimeric amine groups' second edge to engage with other ferrocene signaling moieties.

3.3.2. Aptamer-based electrochemical biosensor

The electrochemical aptamer-based sensors saw a surge in interest after Xiao et al. built the first aptamer-based sensor in 2005 (Xiao et al., 2005). In this work, aptamers that have been transformed on the gold electrode surface undergo conformational rearrangement changes when they bind to ligands. This results in a significant transfer of electrons between the electrodes-bound aptamers and the redox-tagged moiety on the electrode surface (Lubin and Plaxco, 2010). However,

aptamer-based biosensors that are sensitive and selective analysis to direct detection in whole blood (Li, H. et al., 2016a, 2016b), serum (Swensen et al., 2009), and other biological fluids, e.g., dopamine (Farjami et al., 2013), serotonin (Chávez et al., 2017b, 2017a), and other neurotransmitters (Santos-Cancel et al., 2019), are becoming more well-known due to the prompt response and excellent sensitivity.

Recently, Nakatsuka et al. reported a unique concept of an electrochemical biosensing approach for quantifying serotonin by employing molecular recognition (Fig. 6d). Artificial nanopores in quartz nanopipettes having orifices of around 10 nm that are functionalized with aptamers that can reversibly and very selectively detect serotonin (Nakatsuka et al., 2021). Nanopore-based biosensing retains excellent potential for these electronic measurements, in which molecular identification at the single molecule level is made possible via confined intermolecular interactions to nanoscale volume (Fan et al., 2005). In this nanopipette serotonin sensor, the Ion current rectification (ICR) effect causes chemically functionalized serotonin aptamers to be applied to nanopipette wall surfaces to control ionic flux by modifying local charge concentrations and configurations. There are differences in the ion flow because of the pore ion current rectification (ICR) phenomenon, which exists in solutions. In particular, two electrodes separated by conically made nanopipettes are used to monitor the ion current that results from an applied voltage. This event causes an erratic ion flow via the nanopore. As a result, nano-pipettes exhibit non-linear asymmetry that is distinct from ohmic behavior in response to an applied symmetric current-voltage characteristic. Serotonin aptamer-modified nanopipette electrochemical sensors attained great sensitivity, permitting measurements at picomolar concentration. At the nanopipette tip, the physicochemical features that control the sensitivity and selectivity of the response to serotonin analytes are modified by certain chemical interactions between the intended organisms and serotonin aptamers covalently linked to the glass walls. To end this, overall observation ICR, QCM-D, and EIS supported the approach of sensing small molecules via aptamer-modified nanopipettes, where the primary determinant for identifying serotonin is the conformational change of aptamers within the small opening of nanopipettes.

4. Optical biosensors for serotonin

Since its earliest days, supramolecular chemical science has drawn increasing interest because of the abundance of potential new practical applications (Kolesnichenko and Anslyn, 2017). Along with those, supramolecular binders, chemosensors, and innovative molecular probes could revolutionize biosensing and medicinal diagnostics in combination with innovative assays (Mayer and Baeumner, 2019). Until now, biochemical fluid analysis in clinical laboratories has been commonly performed using reliable and well-established techniques like compassion, NMR, GC-MS, and HPLC-MS. However, such techniques cannot be employed in households for routine diagnostic point-of-care testing since they demand a significant investment of time and complex, challenging-to-operate machinery. Molecular recognition-based detection techniques have yielded a variety of promising outcomes in biosensing technology during the past few decades, namely in the area of biological building blocks and immune-based diagnostics (antibody-antigen interactions) (Konstantinou, 2017), genetically modified proteins (Chavan et al., 2019a, 2019b), PCR testing (Greenwald et al., 2018) including DNA and RNA methodology (Mohammadniaei et al., 2019), and enzymatic based diagnosis (Goddard and Reymond, 2004). This section covers the critical development of serotonin molecular sensing, classified into two categories: nano-sensors and chemosensors.

4.1. SWCNT-based optical biosensors for serotonin

This section focuses on optical and electronic-based serotonin identification with SWCNTs to provide information on the biosensing field rapid evolution. We thoroughly examined each SWCNT-based

biosensor's sensitivity, specificity, spatial resolution, and biological compatibility. According to reports from the past few years, SWCNTs have outstanding chemical strategies in their electrical and photo-physical characteristics, attracting them for various electronic applications (Baughman et al., 2002), biosensing (Barone et al., 2005a), imaging (Pu et al., 2014), and molecular transport (Holt et al., 2006). Specifically, SWCNT has surface functionalization schemes such as expanded area surface, proper pore size, and high chemical and mechanical stability. Direct functionalization or coating techniques involving polymers, peptides, or DNA (Giacalone et al., 2016; Ménard-Moyon et al., 2010; Prato et al., 2008). The SWCNTs have distinct structural properties and are flexible nIR (nIR, 900–1700 nm) luminous building blocks for labeled sensors. The wavelength of their nIR fluorescence emission is determined by their carbon lattice structure, which is represented as chirality (n, m) (O'connell et al., 2002). However, nIR fluorescence is exciting due to its transparent biological tissue window, ultra-low background spectral characterization, scattering, and reduced tissue absorption (Hong et al., 2015). The SWCNTs have been successfully utilized as biological sensors for a range of significant chemicals, including proteins, sugars, oxygen-reactive species, and small implying biomolecules (Antonucci et al., 2017; Reuel et al., 2013). For instance, in reaction to the neurotransmitter serotonin, certain DNA-wrapped SWCNTs exhibit changes in their near-infrared (nIR) fluorescence. We reviewed a general program for the development of molecular selection and demonstrated its usefulness through creating a selective nano-sensor based on SWCNT functionalized with serotonin-binding DNA aptamers for neurological molecules serotonin to address the problem of consistently producing neuromodulator serotonin.

Kruss et al. reported the first SWCNT-based biosensors for neurotransmitter detection. An experiment revealed that the presence of the neurotransmitter dopamine causes some ssDNA-SWCNTs to alter in fluorescence (Kruss et al., 2014). The biosensing of neurotransmitters is exceptionally challenging for many reasons like chemical or structural Interfering substance of neurotransmitter similarities to prevent sensitive detection, even though small length scales, short time scales, and lower (nano or picomolar) levels render it challenging to monitor neurotransmitter release on a biosensing device in real-time (He et al., 2016; Kruss et al., 2014). However, the Noncovalent bio-polymer assimilation surface technique is broadly used to functionalize SWCNTs; such a sensible molecular recognition concept was named the "corona phase." Various biopolymers, such as DNA, peptides, surfactants, and lipids, have functionalized the SWCNT's surface (O'connell et al., 2002). Understanding molecular recognition is crucial for medicines, catalysis, and sensor design. This is made possible by the corona phase molecular recognition (CoPhMoRe) (Cho et al., 2009). Importantly, the majority of conventional molecular recognizing patterns are biological macromolecule synthesis, artificial antibodies, and their equivalent in polymeric substances, resulting in a polymer with molecular imprints (Turner and Piletsky, 2005) and aptamers (Ellington and Szostak, 1990). The SWCNT rolled graphene cylinder is a challenging material for the recognition of molecules, transmission of signals, and nIR bandgap illumination with no light-bleaching limitation. They also exhibit environmental sensitivity. Electron-accepting and donating groups can decrease and enhance the emission using sensitivity to individual molecules. There are many developed SWCNTs fluorescence biosensors for β -D-Glucose (Barone et al., 2005a), hybridization of DNA (Jeng et al., 2006), bivalent metal cation (Heller et al., 2006), assorted genotoxins (Heller et al., 2009), nitroaromatics (Heller et al., 2011), nitric oxide (Zhang et al., 2011), protein avidin (Satishkumar et al., 2007) and many others. These efforts have consistently been employed for standard molecular identification agents for enzymes (Barone et al., 2005b), oligonucleotides (Jeng et al., 2006), or certain functional groups that are known to have an affinity for the small-target molecule (Kim et al., 2009). This review demonstrates a recent recognition motif of straightforward interface recognition of -based neuromolecules

serotonin biosensing.

The nIR fluorescent nano-biosensor was established on non-covalently functional SWCNTs with serotonin specifically binding to DNA-aptamer. In 2019, Dinarvand et al. investigated the selective interaction of SWCNT coated with serotonin aptamer interaction with serotonin released using real-time blood platelets (Dinarvand et al., 2019). Here, the SWCNT is wrapped with serotonin aptamer to create a molecular recognition corona-phase disperses the extremely hydrophobic SWCNT in a water-based solution and promotes its interaction with serotonin, and modifies the fluorescence intensity Fig. 7a. Utmost serotonin is collected into blood platelets as dense granules and not across the human brain. Therefore, nIRs fluorescence nano-sensors are placed below serotonin-releasing cells and all combined image secretion of serotonin from platelets with high spatial and temporal resolution Fig. 7a (i-ii). A serotonin-matching aptamer on a SWCNT served as the nIR serotonin nano-sensor, and it reacted to an increased fluorescence intensity of up to almost 80% in PBS solution. By positioning the sensors under and around serotonin-releasing cells, high-resolution pictures of the patterns of serotonin release from individual cells were produced, as shown in Fig. 7a (iii). The fluorescence intensity calibration curve rise, corresponding to a five-parameter logistic level of 1 nM–100 μ M, and the greatest emission peak, the fluorescence intensity was measured (995

nm) shown in Fig. 7a (iv and v). This approach makes it possible to investigate serotonin release with previously unheard-of spatial resolution and to determine the exact time lag between stimulation and release. This determined nIR SWCNT-based nano-sensors imaging procedure under single cells also applies to further study of other neurotransmitters.

According to Jeong et al., in 2019, artificial serotonin addition was discovered in acute CSF slices (Jeong et al., 2019). Through the application of this method, the surface of nIR fluorescent SWCNT signal transducers can evolve synthetic chemical identification on a generic platform. From an extensive library of about 6.9×10^{10} distinct ssDNA sequences, the ssDNA sequence conjugated on SWCNT to show molecular recognition toward neuromodulator serotonin was selected. For polymerase chain reaction (PCR) amplification, two (C) 6-mers and two 18-mer primer regions encircle the ssDNA sequences, as seen in the schematic depiction in Fig. 7b. Each ssDNA-SWCNT constructs $\Delta F/F_0$ is calculated by measuring the intensity of fluorescence at 1195 nm emission 10 s after the addition of the target molecule (F) and the baseline fluorescence intensity prior to the addition of the target molecule (F0). This is done by measuring each construct fluorescence responses to the addition of 100 μ M of serotonin in PBS buffered solution Fig. 7b (i). Next, the near-infrared serotonin probe is used for the

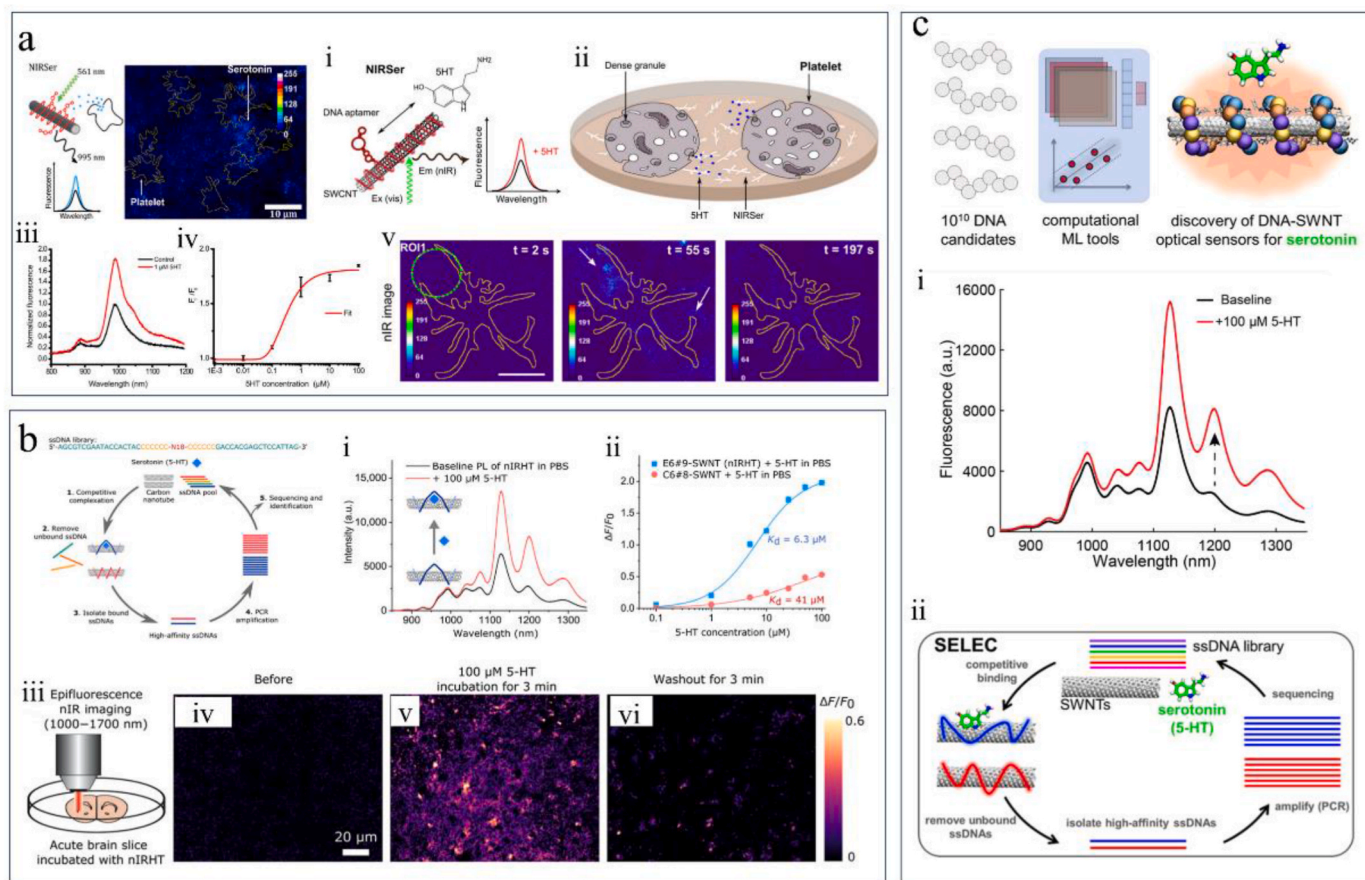


Fig. 7. a) Schematic illustration of nIR fluorescent imaging nano-sensor for single-cell serotonin release. i-v) When serotonin binds to the Ser-aptamer conformation changes, which increases the fluorescence of the SWCNT nIR nano-sensor functionalized with serotonin aptamer. This allows the SWCNT to respond to serotonin only (Dinarvand, M. et al., 2019). Copyright © 2019, American Chemical Society b) The ssDNA-SWCNT-based serotonin nano-sensors. Step-by-step schematic presentation of the SELEC evolution process. i) The fluorescent spectra of ssDNA-SWCNT with and without 100 μ M serotonin added. ii) The serotonin concentration dependence of E6#9-SWCNT and C6#8-SWCNT ($n = 3$). iii) The nIR imaging of a mouse brain slice dorsomedial striatum. (iv, v, and vi) The fluorescence images ($\Delta F/F_0$) depicting an acute striatal brain slice in the same field of view (iv) before, (v) after adding 100 μ M serotonin exogenously for 3 min and (vi) illustration after 3 min of continuous aCSF flow washing (Jeong et al., 2019). c) Schematic illustration of DNA sequences in SWCNT-DNA couples produces a higher serotonin reactivity. E3-P6 sequence fluorescent spectrum before and after 100 μ M serotonin was added to the DNA-SWNT suspension (black trace and red trace, respectively) i) In an experimental setting, serotonin-responsive ssDNAs and distinctly, SWNTs were found selective evolution protocol using SELEC, which was carried out for up to six-rounds. High-affinity single-strand DNAs for fluorescence emission spectroscopy follow-ups of ssDNA-SWNT conjugates pre- and post-adding 100 μ M serotonin (Kelich et al., 2022). Copyright © 2021 American Chemical Society.

serotonin brain imaging. The dynamic range of the near-infrared serotonin probe shows sensitivity to a 100 nM to 100 μ M range of serotonin level. After being exposed to 1 μ M serotonin, the results showed $\Delta F/F_0 = 0.20 \pm 0.03$ with an increased 12.4 signal-to-noise ratio. Relevant near-infrared serotonin probe responsivity toward serotonin to a *Hill-s-equation* illustrates a micro-molar continuous dissociation constant (Kd) for serotonin of 6.3 μ M ($R_2 > 0.99$) Fig. 7b (ii). Near-infrared serotonin probe-labeled slices in CSF were fluorescence-characterized using a specially designed epifluorescence microscope with an extended pass filter of 900 nm to produce infrared fluorescence between 900 and 1700 nm Fig. 7b (iii). Finally, the nIR time-dependent fluorescence image conformation was captured. After capturing a 1-min fluorescence limit and administering 100 μ M serotonin in both the presence and absence, a nIR serotonin probe fluorescence rise of $\Delta F/F_0 = 0.35 \pm 0.26$ (means $\pm$ SD) was detected in Fig. 7b (iv, v, and vi). The developed near-infrared serotonin (ssDNA-SWCNTs) based nano-sensor exhibited a cautious reaction to serotonin compared to metabolites, receptor-targeting pharmacological compounds, and serotonin analogs.

We further review nIR-based DNA-wrapped SWCNT serotonin sensors for potential imaging with a suitable temporal resolution for the regulation of endogenous serotonin. In order to train machine learning algorithms for predicting sequences of DNA with an optical solid response to the neurotransmitter serotonin. In 2021, Kelich et al. studied DNA wrapped on SWCNTs conjugation (Kelich et al., 2022). This approach was designed to train and test classifier models using 18-nucleotide ssDNA segments that have a significant relative infrared fluorescent response when exposed to serotonin upon coupling to SWCNTs. They first used replicas of classifiers using convolutional neural networks (CNN) and second, supported vector machine (SVM) regression models. These DNA models use sequence characteristics to organize ligands as having a high or low reactivity to serotonin. DNA sequences possess the ability to forecast relative values of the spectroscopical response. The images show a developed ssDNA- SWCNT-based molecular recognition toward the analyst's interest in selective attraction that increases optical solid response to the neurotransmitter serotonin. The first 96 unique ssDNA sequences dataset was chosen from a lending library of all possible $\sim 10^{10}$ ssDNA sequences that competitively interact with the SWCNT surface of serotonin. The SELEC approach was developed for a number of collection rounds, each offering data sets chosen in preference of DNA sequences and their abundance shown in the schematic presentation. In Fig. 7c presented most abundant sequence from the experimental group SELEC approach, 3 and 6 rounds, was chosen for serotonin spectroscopic measurements. For 96 different ssDNA-SWNT conjugates, the nIR fluorescence emission was evaluated both before and after 100 μ M serotonin was added. Based on the spectrum of fluorescence emission with the flexibility dominating peak at a central wavelength of approximately 1195 nm, the reaction time of a combination to serotonin was estimated as $\Delta F/F = (F_a - F)/F$, where F stands for before and F_a for after the addition of the serotonin fluorescence signal Fig. 7c (i and ii). Next, the regression model for the sequence of DNA is linked to excellent in quality serotonin for the determination of high or low responses. The sequences were ranked according to the best 10 sequences and their regression-predicted $\Delta F/F$ values with reliably high or low probabilities of being in class 1/class 0 are likewise classed as high reaction while using models created by CNN. The sensor results show that machine learning can quickly identify DNA sequences that respond well to the target serotonin molecule. This can speed up the development of DNA-SWCNT conjugate technologies such as biosensors, bioelectronics, and SWCNT chirality separation.

4.2. Gold nanoparticles-based serotonin biosensor

Gold nanoparticle (AuNP) centered diagnostic analysis provide an attractive and exciting approach for emerging biologically sensing nanoprobe because of their distinctive qualities (Chang et al., 2022; Hepel et al., 2012). Since neurotransmitter molecular recognition units

can easily be functionalized on the surface of AuNPs, they are particularly appealing for application in the development of nano-biosensors (Kr  mer et al., 2022). Especially succinimide estersdithiobis (succinimidyl propionate) (DTSP) (Chavan et al., 2021), 4-mercapto phenylboronic acid (MBA) (Kong et al., 2011), N-acetyl-L-cysteine (NALC) (Godoy-Reyes et al., 2019), and 4-amino-3-hydrazino-5-mercapto-1,2,4-triazol (AHMT) (Feng et al., 2013) were biofunctionalized on the surface of AuNPs for targeting catechol derivatives (Godoy-Reyes et al., 2018b, 2018a). The serotonin detection at μ M concentration in buffer solution at pH 7 by UV-vis titrations spiked in actual blood serum samples was described by Mart  nez-M  n  ez and coworkers. In this study, AuNPs were modified with DTSP, which enables them to interact with serotonin's amino and NALC group. This permits the hydroxyl group in serotonin to attach via hydrogen bonds and electrostatic interactions, resulting in the aggregation of nanosensors. This resulted in a shift in the system's SPR absorption energies that could be measured via spectroscopy and was dependent on the analyte concentration. Their research demonstrated the absence of any colorimetric reaction. Apart from incorporating small molecules into AuNPs, aptamers have also been employed in conjunction with plasmonic particles, yielding positive results for colorimetric neurotransmitter detection at μ M concentrations (Liu et al., 2020). Recently, AuNP-based colorimetric apta-sensor was designed by Chang et al. and coworkers (Ip et al., 2023), and the formation of aptamers and aptamer-target complex resistant to AuNP aggregation produced by chloride. The AuNPs self-aggregate and change color from red to blue when a negatively charged electrostatic stabilization formation forms on their surface due to the coordination of chloride ions and NaCl in the presence of these substances. The colorimetric apta-sensors for serotonin demonstrated good sensitivity and selectivity against possible interferents, with a LOD of 1 ng/mL (5.7 nM) for serotonin.

Very recently, Chavan et al., (2021) reported that exciting new class studies have shown that serotonin adopts the bivalent ligand method because of peroxidative dimerization, which is derived from dimeric structures that may be able to link with several molecules monovalent, which is less advantageous thermodynamically than complex independent recognition sites (Fig. 8a and b) (Chavan et al., 2021). Researchers found that the dimeric result enhanced the catalytic action of one-electrons of serotonin oxidation in the existence of H_2O_2 and horse-radish (HRP) at the C(4) site to the creation of dual phenolic radicals. Huether et al., (1990) reported that dimeric compounds have to form exclusively at the structure of serotonin's C-4 position across the ring of indole (not at the serotonin residue's other location) (Huether et al., 1990). The main reason for using the phenoxy-centered radical manufacturing dimerization structure at serotonin's C(4)-C(4) position is that it may provide two separate identification sites that, in contrast to the monomeric serotonin binding site, offer more complimentary binding interaction (Wrona and Dryhurst, 1991). Adjacent binding sites can be distinguished from one another by their location, which is intrinsically supported by chemicals linked to two required binding moieties that provide a more specialized platform.

The two methods involved in the colorimetric biosensing research study are aggregation complex and dimerization. Two identical serotonin particle complexing molecules selectively act together via radical-radical pairing to form dimeric derivatives. DTSP functionalized GNPs induce the intermolecular interaction of two amine groups supplied by dimeric-serotonin, leading to aggregation, which appears to alter UV-VIS absorption spectroscopic and visual responses. The calorimetric nano-sensor enables susceptible detection of serotonin at the nanomolar concentration in buffer and serum solution LOD of 2.6 and 2.81 nM, and the fastest reaction time (3 min) was achieved for visible detection, respectively. With a selective buffer, the proposed sensor can dynamically detect signals between 100 and 300 nM. Furthermore, the authors provided evidence of the notion by demonstrating how molecular immunosensors used for visible color imaging selectively offer superior visual testing at 2.90 nM levels of detection limits.

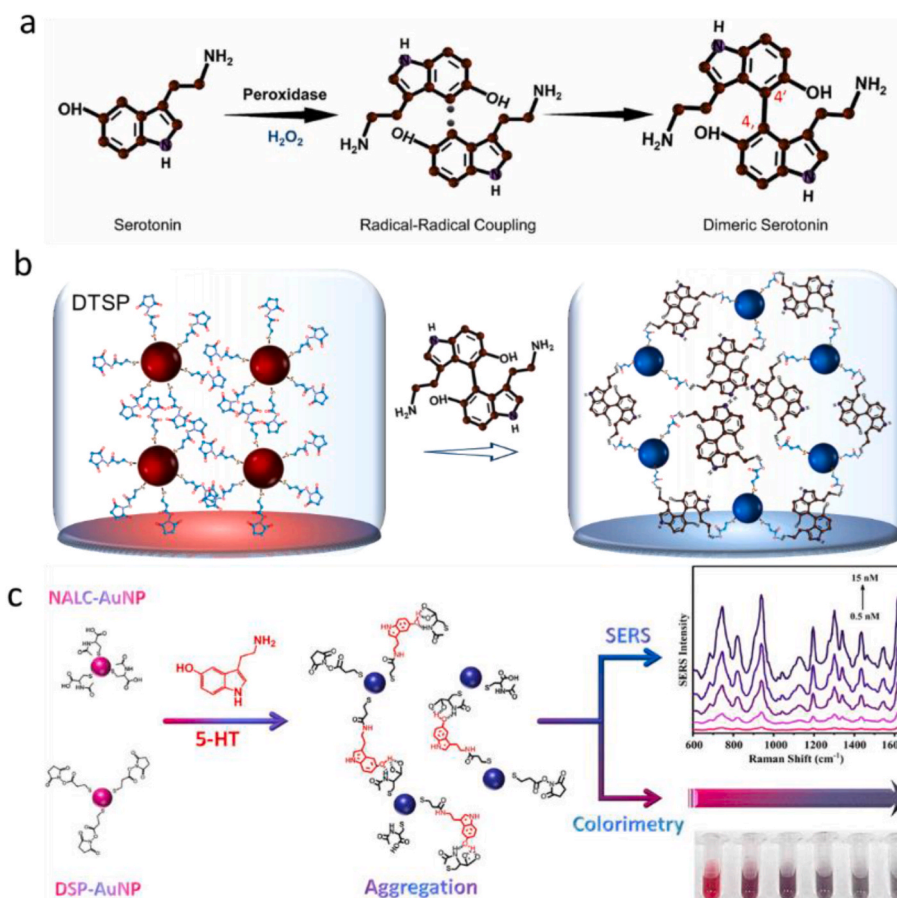


Fig. 8. a) In the presence of a peroxidative substrate (H_2O_2 -HRP), serotonin one-electron oxidation enabled radical-radical coupling to produce a stable dimeric complex. b) Diagrammatic methods based on the scaffold of dimeric serotonin complexing GNPs for colorimetry. Surface and aggregation diagram functionalization of DTSP on GNPs (Chavan et al., 2021). Copyright © 2021 Elsevier c) schematic concept of the dual-mode SERS and colorimetry system for measuring serotonin (Wang et al., 2021). Copyright © 2021 Elsevier.

Wang et al., (2021) reported a colorimetry and Surface-enhanced Raman spectroscopy (SERS) dual-molecule biosensing of serotonin by AuNPs modification Fig. 8c (Wang et al., 2021). This study demonstrated that amino and hydroxyl groups of serotonins interact with DTSP and N-acetyl-L-cysteine (NALC), respectively. Interparticle crosslinking aggregation outcome of the selective connections between the amino and hydroxyl assemblies and functionalized nanoparticles of serotonins caused by these two types of linkers modified AuNPs (DSP-AuNPs and NALC-AuNPs; DSP combines with the amino group of serotonins, whilst NALC uses electrostatic and hydrogen bonding interactions to engage with the hydroxyl group of serotonins). The coupling of plasmon gold particles, the expansion of the SERS "hot spot" region, an apparent color change, and an increase in the SERS signal are possible outcomes of aggregating these two bi-functionalized AuNPs. This double-mode biosensor exhibited a lower detection limit (0.15 nmol L), great sensitivity, respectable selectivity, and determination in serum samples. The RSD range was less than 3.75%, indicating that the sensor had a great attention overlook in determining biological samples.

Similarly, several AuNPs-based simple colorimetric detection methods for the neurotransmitters dopamine and norepinephrine were reported. Kong et al. reported simple dual molecular recognition AuNPs functionalized with both MBA and DTSP linker molecules for interaction diols and amine functional groups of cerebral dopamine with high specificity colorimetric biosensors (Kong et al., 2011). Similarly, Feng and coworker functionalized AHMP-Au nanoparticle as a typical probe, which further induced the accumulation of the AuNPs-AHMT via hydrogen-bond connections, resulting in the colloidal solution in human and urine samples changing from red to blue (Feng et al., 2013). AuNPs

are customized with moieties ended in boronic acid and benzaldehyde to detect the neurotransmitter norepinephrine (Godoy-Reyes et al., 2019). In this work, the gold nanoparticles aggregated at resting apparent color changes from red to blue due to a dual molecular detection system that included either the boronic acid and catechol moiety, or the aromatic aldehyde and amino alcohol group of norepinephrine. However, these methods simultaneously provide simplicity in designing gold particles and establish high specificity and sensitivity colorimetric tests, which provide a straightforward and trustworthy method for monitoring neurotransmitter molecules from a biological fluid.

4.3. Zeolite-based artificial receptors (ZARs) serotonin biosensor

Zeolites are porous crystalline aluminosilicate materials (Ennaert et al., 2016) with highly defined pore dimensions mainly used for catalytic and biomedical applications (Martínez-Martínez and Arbeloa, 2020; Yazdi et al., 2020). Furthermore, a wide variety of artificial zeolites are available, accounting for 70% of the world marketplace. Zeolites are intriguing materials and have many uses, mainly in laundry detergents, adsorbents, and catalysts. This has been made possible by their adsorption qualities, high specific surface area, ion exchange capacity, porous structure, inorganic origin, and thermal stability (Mahmodi et al., 2020a, 2020b). The corner-sharing structure makes up the zeolites framework $[\text{SiO}_4]$ - $[\text{AlO}_4]$ tetrahedra and is often a negative charge, which is balanced by the exchange of cations (such as Na^+ and K^+ ions). Zeolites can, therefore, bond to positively charged chemical molecules, such as diamines or biogenic amines (cadaverine) (Grimm et al., 2021). Zeolite-based artificial receptors (ZARs) are a newly

created flexible approach to receptor creation using microporous hybrid zeolite receptors. Detecting serotonin and other neuro-molecules was possible in biological buffered and real biofluids like urine, serum, and saliva samples. In a recent study, serotonin and dopamine selectively bind to the ZARs (zeolite-based artificial receptors) via the reporter dye-loaded nanopores, taking advantage of both the simple non-covalent identifying motifs and the non-classical hydrophobic effect. They are supported through comprehensive atomistic modeling in conjunction with detailed photophysical and calorimetric experiments as proof of incomparable binding mechanisms. In addition, as reported by Laura et al. (2021) showed that it suitable for high-throughput diagnostics in biological fluids such blood, serum form human, urine, and neurobasal medium, as well as Label-free enzymatic reaction monitoring with two-photon fluorescence imaging (Grimm et al., 2021) (Fig. 9i–iii). The ZARs start to exhibit more significant selectivity of dopamine or serotonin in the existence of similar neuro-molecules such as epinephrine, ascorbic acid, cadaverine, tyramine, histamine, octopamine, phenethylamine, 5-hydroxytryptophan, tryptamine, indole, TrpNH₂, and L-tryptophan neurochemical mixture did not inhibit with the biosensing of dopamine and serotonin.

4.4. Aptamer-based optical biosensor for serotonin

Systematic evolution of ligand molecules through exponential enrichment is an artificially selected procedure to generate synthetic nucleic acid ligands, or aptamers, from oligonucleotide libraries (Tuerk and Gold, 1990). After selection and PCR (polymerase chain reaction) sequencing, aptamers are created chemically via synthesis, allowing unlimited modification to increase their stability and affinity. Aptamers and their matching antibodies may have comparable binding affinities. On the other hand, the benefit of aptamers is their intrinsic stability, which enables them to be subjected to several denaturation and renaturation cycles, facilitating simple sensor surface regeneration.

Numerous sensors based on aptamer have been developed to identify an excess of analytes that are separated from tiny molecules (Swensen et al., 2009) to large-scale cells (Wan et al., 2014), viruses (Covid-19) (Yagati et al., 2023), and microorganisms (Giamberardino et al., 2013; Labib et al., 2013).

Recently, Song et al., 2023 introduced a novel serotonin-responsive aptameric light-up sensor, designing DNA particles with adjustable affinity and achieving dynamical replies on mobile phones for POC testing (Fig. 9b) (Song et al., 2023). In this work, authors constructed allosteric DNA molecular probes and thoroughly examined the structural folding of those probes and ligand binding to aptameric molecules for serotonin recognition. The outcomes demonstrate how different variant mutation locations affect conformational change and sensing reactions. Notably, the changeable aptameric molecules enable the manipulation of affinity and dynamic responsiveness, which can be tailored to various sensing applications with varying threshold levels. They also performed a simple, brilliant phone-based assay that can visualize images of serotonin diagnosis. Developed SERblas have a linearity scale from 10 to 400 nM and a LOD of 5.0 nM under optimal conditions. These values are significantly less than the quantity of serotonin found in typical biological samples such as urine and blood. Moreover, the images and RGB value of the pixels showed an excellent linear correlation with serotonin concentrations between 0.1 and 1 μ M, and the LOD was calculated at 52 nM and 40 nM from the plastic nanosheet. These results indicate that the SERblas method was appropriate for serotonin identification in a readily noticeable way using portable devices.

4.5. Supramolecular serotonin chemosensors

The majority of chemosensors work by forming bonds that are not covalent through interactions like hydrogen bonds and electrostatic bonds, which produce an optical signal when the target element is present. Crucially, because chemosensors quickly adapt (= equilibrate)

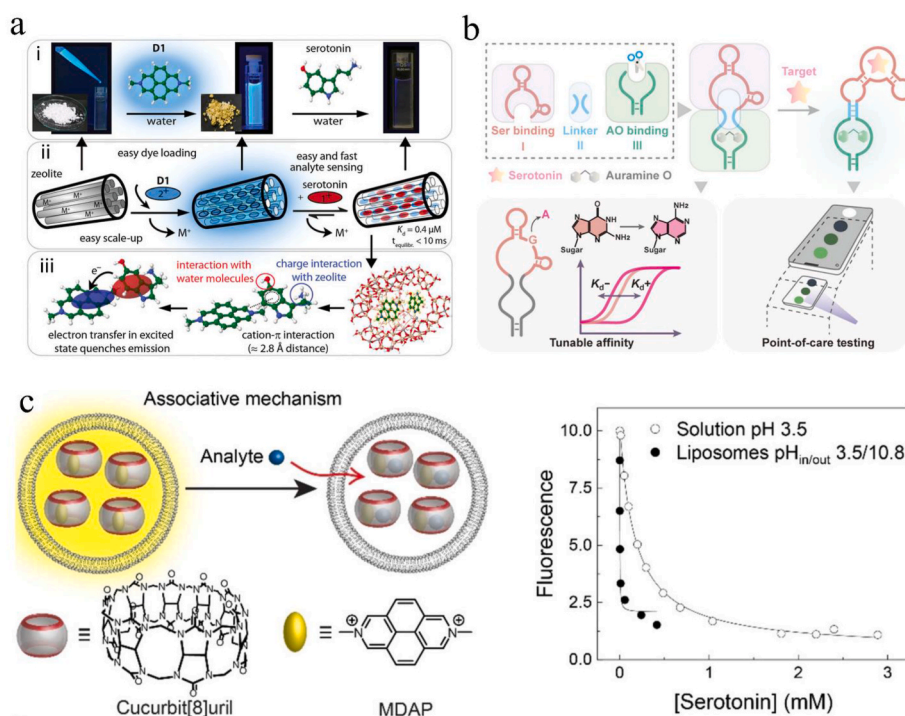


Fig. 9. a) Serotonin detection using zeolites loaded with reporter dye: i) schematic illustration, preparation, and sensing method (Grimm et al., 2021). ii and iii) The binding geometry and emission quenching process between the dye and neurotransmitter in the zeolite channels are determined by total atomistic DFT simulations, which take cavity water molecules into account. b) A schematic representation of a point-of-care test for designer DNA molecules that uses a cell phone to activate SERblas (Song et al., 2023). Copyright © 2023, American Chemical Society c) Liposome-encapsulated supramolecular chemosensor reporter pairs have increased sensitivity in detecting serotonin (Nilam et al., 2022). Copyright © 2022 Angewandte Chemie International Edition published by Wiley-VCH GmbH.

to changes in sample composition, they can be used to monitor biochemical and biophysical processes in real time, such as enzyme reactions and analyte transport through membranes. Molecular probes, on the other hand, usually present an astatic image (Krämer et al., 2022). However, two or more chemical species like host-guest integrated facially and reversibly offer manifold opportunities for developing novel supramolecular chemosensors. The macrocycles such as cucurbit[7]urils (CB7) (Chandra et al., 2020), *p*-sulfonatocalix[n]arenes (C_xn) (Gattuso et al., 2014), or cyclodextrins (CDs) can offer strong affinity for serotonin along with different neuro-molecules with equivalent structures. Considering serotonin plays an essential role as a neurotransmitter associated with depression or specific cancers. A supramolecular encapsulation research for serotonin with CB7 was published by Koner et al. and collaborators (Chandra et al., 2020). The CB7 comprises seven-carbonyl groups presented in both portals of cucurbit[n]urils (CB_n) water-soluble monocyclic molecules, capable of interacting with positively charged molecules or ions (Escobar and Ballester, 2021). As previously pointed out, CB7 and the other host components are spectroscopically silent, and therefore, to further IDA, GDA, or ABA assays for practical biosensing considerations, they must be paired with dyes.

Very recently, Nilam et al., (2022) reported a novel sensing concept using the serotonin molecule as an analyte, liposome-encapsulated reporter pair MDAP (2,7-dimethyldiazapyrenium) and CB8 (cucurbit-[8]uril) (Fig. 9c) (Nilam et al., 2022). The CB8 quenches the fluorescence dye in ternary complexes that it forms with electron-rich, aromatic rings and the fluorescence pigments of MDAP. The authors found the binding constant for serotonin of $K_a = 5.7 \times 10^3 \text{ M}^{-1}$ in a liposome-free traditional fluorescence titration. The outcome shows that low affinity serotonin, about 200 μM , is needed to supply 50 percent of the maximal signaling shift within the CB8/MDAP chemosensory. Because of the outside pH 10.8 and the inside pH 3.5, the maximal signal change was substantially lowered to 7.5 μM . Thus, a substantially better sensitivity (enhancement factor $E_f = 135$) is provided by the liposome-encapsulated CB8/MDAP reporters couple, permitting the detection of serotonin at lower μM levels. This increased the LOD in treated blood samples measured by the CB8/MDAP chemosensory from 120 μM to 1.6 μM .

5. Other biosensors for serotonin

5.1. Field-effect transistor (FET) based serotonin biosensors

This section reviews an in-depth investigation of current developments in FET based serotonin sensors, explaining the interfacial signal conversion, device configuration, materials set, and effectiveness evaluation. The FET conceptual mechanism, a tiny electric field connecting the channel and the gate electrode, allows current to be turned "on" or "off," amplifying the weak current signal (Ferain et al., 2011). An FET typically comprises three terminals: source, drain, and gate electrodes. The source and drain electrodes are separated by a semiconductor channel, and the gate electrode is separated by a dielectric layer (Bandurin et al., 2017). The current The source-drain current (I_{DS}) flow, which is applied to the source and the gate electrode through a contact terminals channel, is modifiable by an electric field that originates from a source-gate voltage sweep (V_{GS}) and is horizontal to the surface of the semiconductor (Cervenka et al., 2015). Several mobile charge carriers in the semiconductor determine how the primary electromagnetic field controls the current I_{DS} (Bandurin et al., 2017). Furthermore, at various V_{GS} , the FET might be in either an "on" or "off" state. The gadget is "off" if the channel conductivity at one V_{GS} is too tiny to flow I_{DS} . The device will turn "on" when the V_{GS} reach a specific value (Dai et al., 2022). During the recent decade, research in 2D FET-based biosensors has attracted appreciable interest due to the possibility of nanoscale downsizing, high sensitivity, analogous biosensing, and the capacity to supply comprehensive biosensing mechanisms (Huang et al., 2021; Mao et al., 2017). The classification summaries of

FET biosensors have different priorities. The most typically utilized technique is based on materials channels, e.g., G-FET (Fu et al., 2017), TMB-FET (Mao et al., 2017), BP-FET (Xia et al., 2014), and 2D organic materials-based sensors (Lee et al., 2017). In this biosensor, The MoS₂/Gr detector is a FET that has a MoS₂-graphene heterostructure channel. A sensor belonging to a different category that has been functionalized using DNA-FET is known as a DNA, aptamer, quantum dot (photodetector), immunological, enzyme, and so many others (Schöning and Poghosian, 2002; Tyagi et al., 2020). Subsequently, FETs are categorized according to the sensing tasks they are used for. Examples of these applications are back-gate and liquid-gate FETs sensors (Azizi et al., 2020), dual-gate FET (Im et al., 2019), electrolyte-gate-FET (GE-FET), and floating-gate FET sensors according to gating modes (Lai et al., 2021).

In particular, the amplifying effect of FET circuits and transduction near the outermost layer of 2D materials are critical components in the optimal signal working principle of 2D-FET biosensors (Mao et al., 2017). FET-based electronic devices are frequently utilized to enhance sensitivity compared to alternative device architectures because gate voltage regulation allows for the modulation of charged carrier mobility (Seo et al., 2020). Microscale and nanoscale features can be incorporated into FET devices, allowing for robust device characterization of charge mobility, substantial carrier species, and conductivity (Stern et al., 2007). However, incorporating materials into FET devices necessitates highly controlled material morphology and sophisticated methods like lithography (Israelachvili, 2011). FET for solution-phase monitoring has mostly been limited to measurements in non-physiologically or low-ionic strength liquids due to its charge-filtering effects (Forsyth et al., 2017). The methods used to overcome these restrictions mostly rely on adding antibody receptors and desalting solutions, which results in a drop in ionic strength (Elnathan et al., 2012), and aptamers (Maehashi et al., 2007), which can improve the effective Debye length next to the FET surface by using transparent polymer coatings to reduce the distance between analytes and the surface (Gao et al., 2016; Meng et al., 2019). Recently, receptors integrated into FET devices have gained attention in the biosensing field as a label-free and susceptible platform for detecting small molecules under high ionic strength. Three electrodes make up FETs, and they are essential transducers that transform signals produced by target recognition events into electrical readouts.

Zhao et al. found that FETs-modified nanoribbons with a serotonin-specific aptamer performed well when exposed to equimolar serotonin levels in a higher ionic strength buffer solution showed more excellent reactions than microribbon FETs (Zhao et al., 2021b). Label-free detection of DNA was carried out using FET biosensors, both micro-and-nanoribbon. On In₂O₃ (and SiO₂), thiolate ssDNA was immobilized. The sensing environment in aCSF was exposed to solutions containing 10^6 – 10^{15} copies of complementary oligonucleotide ($\sim 1 \text{ fM}$ to $\sim 1 \text{ } \mu\text{M}$). On the In₂O₃ (and SiO₂) ribbon, aptamers that detect serotonin alone were covalently immobilized. The 20 μm micro-ribbon FETs modified with ssDNA nanoribbons, which were 350 nm wide, demonstrated greater sensitivity in detecting complementary DNA hybridizations. A large uniform area of In₂O₃ nanoribbon FETs for ions, oligonucleotide, and small-molecule recognition is demonstrated via facile manufacturing, where larger surface-to-volume ratios correspond to improved recognition sensitivity (Fig. 10a).

Nakatsuka et al. most recent discovery involved combining FETs with aptamer-based stem-loop receptors, specifically detecting serotonin, dopamine, sphingosine-1-phosphate, and glucose (Nakatsuka, N. et al., 2018). In this work, serotonin molecules from brain tissue are adaptively detected using a specially designed oligonucleotide stem-loop interface in conjunction with very sensitive aptamer FETs. The sensing device nanometer-thin sheet In₂O₃ FETs were created utilizing techniques that make micro- and nanoscale models easier to scale up for mass production (Fig. 10b). In particular, serotonin aptamer-FETs presented quick responses (approximately in seconds) to broad

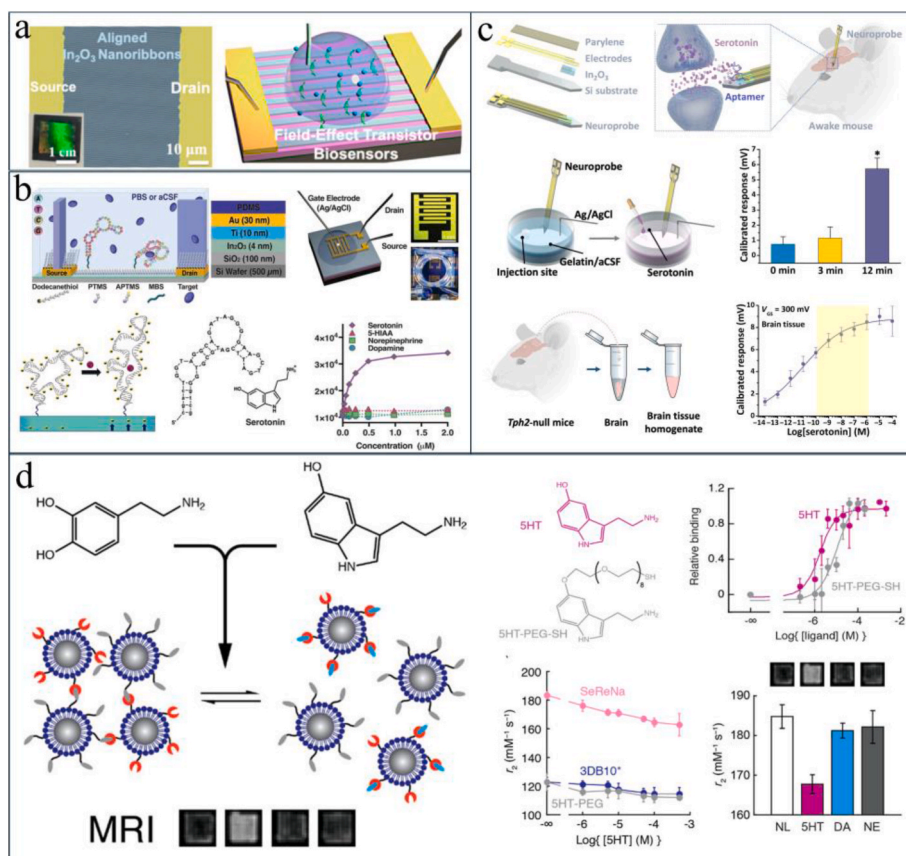


Fig. 10. Schematic illustration of the In_2O_3 nanoribbons FET biosensor for serotonin (Zhao et al., 2021b). Copyright © 2021, American Chemical Society. b) Diagrammatic display of the surface chemistry of FETs. Layers by layers assembly of FETs, pictures captured with a FET microscope, and pictures of the experimental apparatus. The aptamer stem-loops reorient away from semiconductor channels (e.g., serotonin), increasing transconductance (Nakatsuka, N. et al., 2018). Copyright © 2018 Science. c) Layer-by-layer diagrams show how implantable aptamer-FET neuroprobes are designed and used with two FETs at the tip. Here is an example of released serotonin in the extracellular region of a mouse brain implanted with an aptamer-FET neuroprobe for in vivo neurotransmitter monitoring (Zhao et al., 2021a). Copyright © 2021 Science. d) Schematic illustration MRI based serotonin and dopamine biosensors. Titration curves exhibit binding performance similar to that of the 3DB10* derivative of BM3h. The relationship between relaxivity and serotonin concentration for Serotonin-responsive nanoparticle and SPIOs conjugated to 3DB10* or serotonin-PEG-SH alone ([SPIO Fe] = 100 μM). T_2 -weighted MRI (top) and r^2 values of SeReNa samples in the absence of ligand (NL) and with 50 μM serotonin and other neurotransmitter.

spectrums of targets concentrations at (10^{-14} to 10^{-9} M) in physiologically un-diluted artificial CSF. Moreover, serotonin aptamer-FETs continuous exposure of brain tissue for 4 h indicates sensor stability. However, we are focused on this review, how aptamer-functionalized transistors surface for recognizing neurological molecules specially serotonin with similar molecular weights and charge. Different electrical reactions were created by the artificial brain fluid when a single positive charge resulting from the primary amine at physiological pH was observed. On the one side, dopamine aptamer-modification FETs showed a lower current when dopamine concentration increased. In contrast, serotonin aptamer-modified FETs displayed increased current when serotonin was added. This observation suggested that the central signal transducer is the distribution of charges at the FETs surface influenced by the conformational dynamics of the aptamer following target identification. The main goal of this work is to investigate aptamer conformational changes that affect surface densities and chemistries and potentially raise the signal-to-noise ratio between specific and non-specific binding reactions. In order to comprehend the electronic observation in the capacitive sensing platforms, aptamers connect with small molecules. Recently, Zhao et al. and coworkers reported FET modified with an implanted aptamer for electronic small molecule monitoring serotonin (in vivo) under high ionic strength conditions (Fig. 10c) (Zhao et al., 2021a, 2022). The sensing platform was differently produced utilizing technology for high-throughput microelectromechanical systems (MEMS), where Si-based implantable

neuropores with In_2O_3 FETs ultrathin semiconductor film ($\sim 3\text{--}4$ nm) modified with serotonin aptamer to recognize serotonin reported in vivo with minimal biofouling. Neuro-probes were shank tips of either 150 or 50 μm in width and thickness and were assembled on 4-inch Si wafers. These larger neuro-probes were planted in awakened live rats, wherein they identified electrically excited serotonin releases with high target sensitivity. However, in vivo measurements have been presented up to now (electrical stimulation after and before serotonin in the mouse brain), and only $\sim 10\text{--}20$ data points were collected within a few minutes. The experimental analysis demonstrated that the sensor could detect serotonin between 100 μM and 10 fM concentrations. It is important to remember that when the aptamer is attached to the target molecule, a conformational shift in the negatively charged aptamer backbone triggers the biosensing mechanism. The outcome showed that voltage-gated semiconductors detect surface charge redistribution. This neuro-sensing mechanism may be used as a universal technique for identifying tiny neuromolecules since it is not dependent on the charge or electrochemical characteristics of the target molecule.

Furthermore, Nishitani et al. described the modification of an Au-gate FET biosensor by a skillfully crafted nano filter layer to improve the signal-to-noise (S/N) ratio to detect serotonin, a neurotransmitter sensitive to stress. (Nishitani and Sakata, 2020). This schematic allows nano-filter capture on film preparation on the gold surface by adding the diazonium-aryl salt decline strategy and a tendency for boronation. This study shows that phenylboronic acid (PBA) in the nano-filter functions

as a receptor to collect interfering small molecules and simply serotonin can come into contact with the gold sensor interface and create an electrical signal via aryldiazonium salt chemistry. This potentiometric biosensor displayed a linearity to serotonin in the range of 0.6–2 μM in blood, with a sensitivity of 23 mV/decade. While individual neurotransmitter tracking, such as dopamine and serotonin, has advanced significantly due to these investigations, it is still difficult to simultaneously monitor many brain chemicals with molecular specificity and spatiotemporal precision.

Due to their superior electron-transfer platforms, surface-active sites, sticking bond-free surface, wide surface area, and atomic smoothness, layered inorganic materials such as MoS_2 , RuS_2 , Bi_2WO_6 , and SrBrO nanoparticles are very desirable for biosensing applications (Veeralingam and Badhulika, 2020a; Recently, Veeralingam et al., 2020 reported a highly selective and quick serotonin sensor using a high-performance FET biosensor based on Al-modified $\beta\text{-Bi}_2\text{O}_3$ nanofibers. The remarkable electrochemical properties of the scattered multidimensional surface and the regulation of the Debye screening length using a back-gate electrode enabled the Bio-FET to exhibit remarkable serotonin sensitivity (51.64 $\mu\text{A}/\text{nM}$) with a limit of detection of 0.29 nM. Furthermore, the sensor successful real-time urine sample recognition suggests a potential application for point-of-care diagnostics. Sinha et al. reported that in order to obtain an ultrasensitive, real-time, and rapid diagnosis, multidimensional direct serotonin molecular fingerprinting on the outer layer of ZnO nanorod device connected with FET setup is a cost-effective approach that has a great deal of potential for translation to clinical settings (Sinha et al., 2023). With screen-printed electrodes, this method has boosted the threshold for detection limit in a physiological analyte to 0.1 fM with a linear scale of 0.1 fM to 10 pM in real-time, enabling the practical bulk manufacture of sensors for validation in clinical trials. However, these quantities of serotonin monitoring in the presence of a gate-based electromagnetic field are efficiently established by FET-based biosensors. It is possible to achieve excellent selectivity, sensitivity, quick response, helpful applicability, and repeatability by using an inexpensive fabrication platform. Furthermore, back gate FETs that avoid interference with the sample and have an accurate electrical signal response are very beneficial.

5.2. Magnetic resonance imaging (MRI) based serotonin biosensors

Molecular imaging has emerged as the most sophisticated sensing technique in noninvasive imaging modalities, opening up a world of possibilities for molecular therapeutic and diagnostic applications (Hoffman and Gambhir, 2007). The terms "imaging" are widely used to describe biological combination processes that take place in vivo and use imaging molecules to produce both structural and functional molecular visualization with the use of certain imaging probes (Ametamey et al., 2008). Molecular imaging has applications in drug efficacy research, early diagnosis, characterization, and "real-time" illness monitoring (Lee et al., 2010). MRI is the most widely applicable technique for neurochemical mapping (Angelovski and Tóth, 2017), primarily provides an alluring blend of little invasiveness and the capacity to track extended brain measurement (Wei et al., 2021), and moderately high-resolution imaging in biological tissue with depth penetration analysis in animals and humans (Hsieh et al., 2019). Functional magnetic resonance imaging (fMRI) primarily targets the ventral striatum, a brain region that integrates several anatomically defined neurotransmitters involved in behavior motivation and increases blood volume and flow (Lee et al., 2014). Shapiro et al. developed MRI contrast agents sensitive to neurotransmitters that could design dopamine and serotonin signaling in active brains (Shapiro et al., 2010). The sensor devices in question are modified versions of BM3h, a protein with a paramagnetic heme domain that modifies T_1 -weighted MRI data. However, the BM3h sensor variant called BM3h-9D7 displays optimal specificity for serotonin (dissociation constant $K_d = 70 \mu\text{M}$) and other neurotransmitter such as dopamine ($K_d = 1.3 \mu\text{M}$) and norepinephrine ($K_d = 37 \mu\text{M}$) (Brustad

et al., 2012). According to Jasanoff et al., a different kind of molecular-level fMRI investigation was conducted using the serotonin-sensitive mutant BM3h-2G9C6 to map serotonin transport at the micron size in living animals. Due to the iron-coordinated replacement of serotonin by a water molecule, the serotonin reuptake could be seen once the sensor relaxivity increased. This MRI-detectable serotonin sensor improved MRI signal which exhibits a 0.7 mM serotonin dissociation constant with over 200-fold specificity against norepinephrine and dopamine (Brustad et al., 2012). This research demonstrated substantially resolved estimates of serotonin elimination rates in vivo analysis, compartmental modelling in combination with a multidimensional mapping of serotonin transport in rat brains, and molecular imaging using this probe.

In 2019, Jasanoff et al. and colleagues testified an MRI-based competitive binding approach applying superparamagnetic iron oxide (SPIOs) nanoparticles to detect serotonin and dopamine (Hsieh et al., 2019) (Fig. 10d). These MRI-based performances, even sub-nanomolar particle levels, were compelling and highly sensitive for neurotransmitter biosensing. The researchers functionalized two different types of SPIO nanoparticles using tyramine or bacterial cytochrome P450-BM3 heme domain proteins (BM3h). The interaction of BM3h with tyramine caused nanoparticles to agglomerate, which darkened the MRI signal. The particle clusters were broken up along with a brightening of the MRI signal when neurotransmitters with a higher affinity for BM3h were present. These findings show that neurotransmitters can be conjugated to binding proteins and cognate-tethered neurotransmitters to SPIOs to build neurotransmitter sensors for T_2 -weighted MRI signal. Importantly, this displacement-based approach allowed at μM concentration detection of serotonin and dopamine in rat brains, demonstrating high sensitivity and robustness for prospective in vivo applications.

In this overview, we studied methods for serotonin detection of critical human biomarkers in different biological samples. The graphical abstract's picture indicates that distinct "labels" or "label-free" approaches may be used for biomarker detection. A thorough review of the literature was done to determine the many approaches utilized to detect serotonin in human body fluids, animal experiments, and buffer solutions. The detailed survey results contain optical and electrochemical methods for serotonin detection, including the year, technique used, recognition strategy, biofluid medium, detection sensitivity limits, and linear range are shown in Table 2.

CV (Cyclic voltammetry), DPV (differential pulse voltammetry), CA (chronoamperometry), potentiometric (PMC) poly(3,4-ethylenedioxy thiophene), carbon nanotube (CNT), m-aminophenyl boronic acid (AniBA), zinc oxide (ZnO), AC voltammetry (ACV), Square Wave Voltammetry (SWV), GCE (Glassy carbon electrode), Screen printed carbon electrode (SPCE), carbon cloth (CCT), Field-effect transistor (FET), Colorimetric (CM), Fluorescence spectrometer (FS), Fetal bovine serum (FBS), phosphate buffer (PB), Artificial serum (AS), artificial cerebral spinal fluid (aCSF), Rabbit brain tissue (RBT), Gold Electrode (AuE), Gold nanoparticles (AuNPs), Platinum nanoparticles (PtNPs), Carbon paste electrode (CPE).

6. Conclusion and future perspectives

Since the discovery of serotonin, numerous technologies have been created to remove the shadow of problems surrounding these neuro-molecules. The principal use of these instruments is to examine the links between serotonin neurotransmitters and behavior to awareness of the mechanism of serotonin regulation. It is also helpful in dealing with serotonergic disorders and developing effective therapies. In order to understand serotonin role in disease development, it is necessary to develop serotonin diagnosis methods appropriate for long-standing and in vivo dimensions. Among the techniques we investigated, electrochemical and optical biosensing strategies performed better after employing a variety of nanomaterials, DNA, and aptamers focused on miniaturization and cost-effectiveness. In clinical analysis, diagnosis

Table 2
Summary of different Optical and electrochemical methods for serotonin detection.

Detection System	Recognition Materials	Recognition Methods	Technique Used	Electrode	Biological Source	Limits of Detection (LOD)	Sensitivity	Linear Range	Ref.
Electrochemical Biosensor for Serotonin	Nanomaterials-based Biosensor	Graphene oxide (rGO-Ag ₂ Se)	DPV	GCE	buffer and serum	29.6 nM	–	0.1–15 μ M	Panneer Selvam and Yun (2020)
		AgNP-rGO/Pt	DPV	GCE	Urine	0.078 nM	–	0.0001–100 μ M	Moslah et al. (2021)
		Ni NPs-rGO/GCE	CV	GCE	Urine	0.01	–	0.02–2 μ M	Ran et al. (2021)
		Silver/polypyrrole/copper oxide (Ag/PPy/Cu ₂ O)ternary nanocomposite	DPV	GCE	Human blood	0.0124 μ mol L ⁻¹	–	0.01–250 μ mol/L	Selvarajan et al. (2018)
		Nanoplatfrom based on Ppy and Au NPs	DPV	GCE	Serum	33.22 nM	0.3316 μ A μ M ⁻¹	0.1–15 μ M	(Tertiş et al., 2017)
		Polymelamine modified edge plane pyrolytic graphite sensor (EPPGS)	SWV	–	Urine and Blood	30 nM	0.088 μ A μ M ⁻¹	1–100 μ m	Gupta and Goyal (2014)
		Tungsten trioxide (GI-WO ₃) nanoparticles exposed to gamma radiation	DPV	GCE	Blood	1.42 nM	–	0.01–600 μ M	Anithaa et al. (2017)
		Graphene encapsulated AuAg alloy (AuAg-GR) nanohybrid	Amperometry	ITO	Serum	1.6 nM	0.76 μ A/ μ M	0.1–700 μ M	Thanh et al. (2017)
		Cobalt oxide nanotubes with graphene oxide (rGO-Co ₃ O ₄)	DPV	GCE	–	1.13 nM	0.13 μ A/ μ M	1–10 μ M	Shahid et al. (2019)
		Au-Nanostar//g-C ₃ N ₄	SWV	GCE	Urine, serum	15.1 nM	–	0.5–1000 μ M	Kumar et al. (2023)
	SWCNT-based Biosensor	AuNPs- modified CNT with 2-amino-5-mercapto-1,3,4-thiadiazole (AMT)	SWV	GCE	Human Serum	7.8 nM	–	0.015–5 μ M	Shekher et al. (2023)
		PEDOT/PSS	DPV	GCE	Human Serum	10	4.9 μ A μ M ⁻¹ cm ⁻²	0.05–2.15 μ M	Coyle et al. (2024)
		CNTs-ionic liquids composite gel modified	DPV	GCE	Blood serum	8 nM	–	20 nM to 7 μ M	Sun et al. (2009)
		PtNPs deposition on the (CNTs-Cu ₂ O-CuO)	CV	GCE	Serum and urine	3 nM	–	15 nM to 3 mM	Ashraf et al. (2021)
		PEDOT/CNT/AN	DPV	CNT	Live cells	50 nM	0.42 μ A/ μ M	1–100 μ M	(Li, Y.-T. et al., 2016)
		AuNPs-MPA-(PDDA-oSWCNTs-5-HT apt) ₂ -PDDA-o SWCNTs-Tyr	DPV	SPCE	Patient serum	2 nM	5.761 & 0.734 μ A/ μ M/cm ²	0.05–0.5 μ M	Li et al. (2021)
		AuNPS-modified indium tin oxide (NGITO) electrode system	SWV	GCE	Urine	32	–	1–20 μ M	Goyal et al. (2008)
		Intercalated graphite electrodes	DPV	–	RBT	0.2 μ M	1.89 μ A μ M ⁻¹	0.1–100 μ M	Wang et al. (2003)
	MWCNT-based Biosensor	RuO ₂ NWSeCeO ₂ -AuNFs/GO/ (Nafion/Ni(OH) ₂ -MWNTs/ DHP film-coated electrode	DPV	SPCE	CSF, serum, & plasma	160 nM	–	0.01–150 μ M	Samie and Arvand (2019)
			CV, DPV & CA	GCE	Buffer solution	0.003 μ M L ⁻¹	–	0.008–10 μ M L ⁻¹	Babaei and Taheri (2013)
			DPV	GCE	Blood	5 $\times$ 10 ⁻⁹ mol/L	–	2 $\times$ 10 ⁻⁸ to 5 $\times$ 10 ⁻⁶ mol/L	Wu et al. (2003)
		MWNTs-SiO ₂ -chitosan	SWV	SPCE	Rat CSF	0.01 μ M	–	0.1 μ M–2 μ M	Wang et al. (2016)
		Fe ₃ O ₄ -MWCNT-PBCG	DPV	GCE	Serum	80 nM	–	0.5 μ M–100 μ M	Ran et al. (2017)
	MXene based Biosensor	FeC-AuNPs-MWCNT/ SPCE	SWV	SPCE	Urine	17 nM	–	0.05–20 nM	Wu et al. (2022)
		Chitosan and carboxylated MWCNTs	DPV	GCE	Saliva	10 μ M	–	9–1000 μ M	Tang et al. (2023)
		Ti ₃ C ₂ T _x -reduced oxide graphene Nanocomposite	CV	GCE	Human Blood	10 nM	–	0.025–147 μ M	Su et al. (2022)

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Table 2 (continued)

Detection System	Recognition Materials	Recognition Methods	Technique Used	Electrode	Biological Source	Limits of Detection (LOD)	Sensitivity	Linear Range	Ref.	
Optical Biosensor for Serotonin	Dimerization	MXene with an L-cysteine termination silver nanoplate	DPV	GCE	Blood	0.08 μM	–	0.5–150 μM	Chen et al. (2021)	
		MXene/SWCNTs nanocomposite	CV	GCE	Cell line	1.5 nM.	–	4 nM-103.2 μM	Jiang et al. (2022)	
		Nb ₂ CT _x /PCN/CCT	DPV	CCT	Serum	63.24 nM	–	1–100 μM	Mufeeda et al. (2023)	
		Simply DTSP modified screen printed gold-electrode	DPV	SPCE	Buffer Human serum	0.9 nM 1.4 nM	2.0 × 10 ^{−2} nM	10 to 400	Chavan et al. (2022b)	
		Aptamer based Biosensor	Serotonin-responsive binary light-up aptameric sensor (SERblas)	SF	–	5% Urine 1% serum buffer	9.8 nM 7.1 nM 5.0 nM	–	10–400 nM 10–400 nM 10–400 nM	Song et al. (2023)
			Fc-labeled serotonin aptamer immobilized on gold electrode.	DPV	–	CSF	0.3 μM	–	1 μM–100 μM	Li et al. (2022)
			Methylene blue (MB) labeled aptamer	ACV	Au E	Blood	0.017 fM	–	1 pM–10 nM	Geng et al. (2021)
			Aptamer/MCH	DPV	SPCE	Blood	5.6 nM	–	25–100 nM	Ahmad et al. (2023)
		Antibody based Biosensor	SPE/GO-chitosan/anti-serotonin Ab	DPV	GCE	Serum, Saliva, Tear & Urine	3.2 nM	0.05 μA/μM	0.01–100 μM	Adumitrăchioaie et al. (2019)
		Enzyme based Biosensor	Tyrosinase immobilization on carbon nano-powder and electrode modified with cobalt (II) phthalocyanine.	CV	CPE	PB, and walnut samples	0.84 M	0.2034 A M ^{−1}	4–140 M	Apetrei and Apetrei (2013)
	SWCNT-based Biosensor	Serotonin-binding-aptamer-SWCNTs FI increase	FS	–	Release from human blood platelets	–	100 nM to 10 μM	100 nM and 1 μM	(Dinarvand et al., 2019)	
	Nanoparticle based Biosensor	Screening approach Identification of polynucleotides by exponential enrichment for selective ssDNA-SWCNTs	FS	–	Brain slices of mice and exogenous addition of serotonin	–	100 nM-50 μM	100 nM to100 μM	(Jeong et al.)	
		Biofunctionalized AuNPs with DSP and NALC	CM	–	Blood serum	0.12 μM	–	0–3 μM	(Godoy-Reyes et al., 2018)	
		Dimeric-serotonin bivalent ligand-modified AuNPs	CM	–	Serum	2.6 nM	–	100–300 nM	Chavan et al. (2021)	
		DSP-AuNPs&NALC-AuNPs	CM/SERS	–	Serum	0.15 nM L ^{−1}	–	0.5–1500 nM L ^{−1}	Wang et al. (2021)	
		Protein-templated fluorescent gold nanocluster based biosensing.	FS	–	Human serum	0.049 μM	–	0.2 μM–50 μM	Wang et al. (2018)	
		Plasmonic via SA-AuNPs	CM	AuNPs	Human plasma	0.02 μM	–	0.05–1.0 μM	Avci et al. (2024)	
		Transferrin encapsulated gold nanoclusters (Tf-Au NCs)	FS	–	Serum	0.049 μM	–	0.2–50 μM	Sha et al. (2019)	
		Fluorescence (QDs@SiO ₂ @MIPs)	FS	–	2.5 Serum	0.69 ng/mL	–	0.3–2.8 μ (50–500 ng/mL)	Wang et al. (2018)	
		Aptamer-based Biosensor	Base Pair Technologies	colorimetric	–	Fetal bovine serum (FBS)	0.3 μM	–	0.75–2.5 μM	(Chávez et al., 2017)
			Aptamer-capped AuNP	CM	–	FBS	300 nM	–	0.8–2.5 μM	(Godoy-Reyes et al., 2018)
		serotonin aptamer and its complementary strand	colorimetric	–	Blood	2.2 nM	–	–	Tran et al. (2024)	

(continued on next page)

Table 2 (continued)

Detection System	Recognition Materials	Recognition Methods	Technique Used	Electrode	Biological Source	Limits of Detection (LOD)	Sensitivity	Linear Range	Ref.
Other Biosensor for Serotonin	Nanomaterials Modification	Serotonin-responsive binary light-up aptameric sensor (SERblas)	FS	–	Urine Serum Buffer	9.8 nM 7.1 nM 5.0 nM	–	10–400 nM 10–400 nM 10–400 nM	Song et al. (2023)
		Al functionalized β -Bi ₂ O ₃ nanofibers.	FET	–	Urine	0.29 nM	51.64 μ A/ nM ^{–1}	10 nM–1 μ M	Veeralingam and Badhulika (2020b)
		AuNPs/m-AniBA)/ polyaniline (pAni) functionalization	PMC	Au surface	Serum albumin	0.82 nm	–	32.7–93.7 mV/decade	Nishitani et al. (2022)
		MIP-coated ZnO nanorod-based FET biosensor	FET	SPCE	Human serum	0.1 fM	–	0.1 fM–10 pM	Sinha et al. (2023)
		Modified thin-film In ₂ O ₃ FETs with deoxyribonucleotide aptamers,	FET	–	aCSF	10 fM	–	10 fM–1 nM	(Nakatsuka et al., 2018)
		Extended gate Au-FET, (EG-Au-FET) label free biosensor	FET	–	Blood	0.6 μ M	23 mV/decade	0.6–2 μ M	Nishitani and Sakata (2020)
		FET gated biosensor based on conducting polymer nanohybrid immobilized with aptamer	FET	–	AS & aCSF	10 fM	–	10 fM–100 nM	Lim et al. (2022)
		Zinc oxide (ZnO) FET-based detection	FET	–	Serum	0.1 fM	–	0.1 fM–1 nM	Sinha et al. (2021)

research, and quality control, most electrochemical and optical serotonin biosensors identified samples with excellent accuracy, high sensitivity, and sufficient selectivity, making them valuable instruments. The relatively ancient phylogenetically based serotonin systems have been defended through transformation due to their functions acting as many fundamental mechanisms, such as breeding, sustaining, and homeostasis. As progression developed, serotonin systems in both the CNS and periphery attained prolonged roles in the human body, regulating the state of mood, depression, cognition, and a variety of other diseases (irritable bowel syndrome, psychiatric disorders, Alzheimer's disease, endocrine disorders, and emotions).

Serotonins are neuromolecules that are crucial for preserving both physical and mental well-being. Even smaller variations in their concentrations in bodily fluids could indicate the existence of a number of illnesses, such as neurological and cardiovascular issues. Therefore, one needs to understand the multiplicity of functions according to this simple neurotransmitter serotonin molecule, and the development of susceptible and rapid diagnosis tools can offer a practical means of keeping an eye on serotonin levels in the human body. Improved sensing and biosensing platforms that make use of surface modification of nanomaterials graphene quantum dots, carbon nanotubes, or gold nanoparticles produce better results, faster reaction times, and more compact devices. Numerous nanomaterials have optical and electrical characteristics that make them immediately applicable to serotonin detection; additionally, they can be tailored to meet particular needs and specifications. As this review has shown, aptamer serotonin at reduced quantities improves illness treatment, prevention, diagnosis, and the healthcare system as a whole.

Since their discovery almost 20 years ago, modifications of CNTs, SWCNTs, and MWCNTs have also been discovered. Numerous extensive uses for these technologies imply that CNT-based technologies will have unique qualities such as higher mechanical strength, excellent aspect ratio, extraordinary electrical conductivity, and nanoscale diameter. The fabrication, construction, and performance of CNT-based biosensors detecting serotonin in serum or urine are presented. The high sensitivity and selectivity electrochemical method is a practical approach among numerous detection technologies. In addition, it shows fast response, high reliability, and low cost. More importantly, there is much research

that concentrates on serotonin analysis in actual samples, but there are not many that deal with serotonin analysis in real-time. The unique nIR window (900–1700 nm) in which DNA-aptamer SWCNTs glow lowers photon scattering and increases imaging penetration depths. In situ or in vivo measurement of serotonin, particularly in human blood platelets, is clinically significant for diagnosis purposes. Modified SWCNTs can be used to image chemical communication between cells and further increase signal/noise nIR fluorescence nanosensors for serotonin. SWCNTs have also demonstrated their more significant potential as adaptable components for serotonin biosensors. In order to study serotonin neuromodulation, high spatiotemporal fluorescence imaging probes with reversibility, photostability, sub-micrometer spatial resolution, and selectivity against serotonin metabolites and receptor-targeting medications are offered by SWCNT-based biosensors, which also offer a rich chemical playground. FET-based sensors have garnered significant interest in point-of-care (POC) diagnostics due to their exceptional selectivity and quick detection compared to other serotonin detection techniques. FET biosensors have a high sensitivity to serotonin detection; nevertheless, in highly ionic physiological samples, the ionic screening effect and other interfering factors frequently impede the biosensing capability. In addition, dimeric serotonin-based optical and electrochemical detection strategies are highly suitable for various bioanalytical applications.

This review will be highly beneficial for researchers focused on serotonin biosensing. By compiling and analyzing a wide range of recent advances in the field, we provide a comprehensive overview of the latest optical and electrochemical detection methods for serotonin. These methods involve cutting-edge technologies, including 2D nanomaterials, DNA, aptamers, and advanced electrode designs, tracing their development from initial concepts to state-of-the-art applications.

We also delve into the fundamental principles that underpin the functionalization of these materials, which are critical for enhancing the performance of biosensors. This review is intended to inspire the development of new approaches that improve the accuracy, selectivity, and sensitivity of serotonin detection. Such advancements are particularly important for in vivo studies and the creation of portable devices for practical, real-world applications.

Although these detection techniques are only beginning to shed light

on the mechanisms of serotonergic activation, the most advanced technologies show promise in distinguishing individual neuron activity and providing more precise measurements of serotonin levels. Until these methods are fully developed and implemented, researchers will continue to explore, innovate, and refine approaches to better understand serotonin's complex role in various biological fluids, including cerebrospinal fluid (CSF), urine, saliva, blood, plasma, serum, and the brain.

CRedit authorship contribution statement

Sachin Ganpat Chavan: Writing – original draft, Investigation, Formal analysis. **Pooja Ramrao Rathod:** Data curation, Conceptualization. **Aneesh Koyappayil:** Writing – original draft, Resources, Methodology, Conceptualization. **Seowoo Hwang:** Methodology, Investigation. **Min-Ho Lee:** Writing – review & editing, Supervision, Project administration, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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References

- Abbaspour, A., Noori, A., 2011. A cyclodextrin host–guest recognition approach to an electrochemical sensor for simultaneous quantification of serotonin and dopamine. *Biosens. Bioelectron.* 26 (12), 4674–4680.
- Adumitrăchioaie, A., Tertiș, M., Suciu, M., Graur, F., Cristea, C., 2019. A novel immunosensing platform for serotonin detection in complex real samples based on graphene oxide and chitosan. *Electrochim. Acta* 311, 50–61.
- Ahmad, H.M.N., Andrade, A., Song, E., 2023. Continuous real-time detection of serotonin using an aptamer-based electrochemical biosensor. *Biosensors*.
- Aizenstein, M.L., Korf, J., 1979. On the elimination of centrally formed 5-hydroxyindoleacetic acid by cerebrospinal fluid and urine. *J. Neurochem.* 32 (4), 1227–1233.
- Amara, U., Hussain, I., Ahmad, M., Mahmood, K., Zhang, K., 2023. 2D MXene-based biosensing: a review. *Small* 19 (2), 2205249.
- Ametamey, S.M., Honer, M., Schubiger, P.A., 2008. Molecular imaging with PET. *Chem. Rev.* 108 (5), 1501–1516.
- Amireault, P., Sibon, D., Côté, F., 2013. Life without peripheral serotonin: insights from tryptophan hydroxylase 1 knockout mice reveal the existence of paracrine/autocrine serotonergic networks. *ACS Chem. Neurosci.* 4 (1), 64–71.
- Angelovski, G., Tóth, É., 2017. Strategies for sensing neurotransmitters with responsive MRI contrast agents. *Chem. Soc. Rev.* 46 (2), 324–336.
- Anithaa, A.C., Asokan, K., Sekar, C., 2017. Highly sensitive and selective serotonin sensor based on gamma ray irradiated tungsten trioxide nanoparticles. *Sensor. Actuator. B Chem.* 238, 667–675.
- Antonucci, A., Kupis-Rozmysłowicz, J., Boghossian, A.A., 2017. Noncovalent protein and peptide functionalization of single-walled carbon nanotubes for biodelivery and optical sensing applications. *ACS Appl. Mater. Interfaces* 9 (13), 11321–11331.
- Apetrei, I.M., Apetrei, C., 2013. AMPEROMETRIC TYROSINASE BASED BIOSENSORS FOR SEROTONIN DETECTION.
- Ashraf, G., Asif, M., Aziz, A., Ifthikhar, T., Liu, H., 2021. Rice-Spikelet-like copper oxide decorated with platinum stranded in the CNT network for electrochemical in vitro detection of serotonin. *ACS Appl. Mater. Interfaces* 13 (5), 6023–6033.
- Avci, B., Akpınar, Y., Ertay, G., Volkan, M., 2024. Sialic acid-functionalized gold nanoparticles for sensitive and selective colorimetric determination of serotonin. *ACS Omega* 9 (22), 23832–23842.
- Azizi, A., Dogan, M., Long, H., Cain, J.D., Lee, K., Eskandari, R., Varieschi, A., Glazer, E. C., Cohen, M.L., Zettl, A., 2020. High-performance atomically-thin room-temperature NO₂ sensor. *Nano Lett.* 20 (8), 6120–6127.
- Azzouz, A., Goud, K.Y., Raza, N., Ballesteros, E., Lee, S.-E., Hong, J., Deep, A., Kim, K.-H., 2019. Nanomaterial-based electrochemical sensors for the detection of neurochemicals in biological matrices. *TrAC, Trends Anal. Chem.* 110, 15–34.
- Babaei, A., Taheri, A.R., 2013. Nafion/Ni(OH)₂ nanoparticles-carbon nanotube composite modified glassy carbon electrode as a sensor for simultaneous determination of dopamine and serotonin in the presence of ascorbic acid. *Sensor. Actuator. B Chem.* 176, 543–551.
- Bader, M., 2019. Serotonylation: serotonin signaling and epigenetics. *Front. Mol. Neurosci.* 12, 288.
- Baganz, N.L., Blakely, R.D., 2013. A dialogue between the immune system and brain, spoken in the language of serotonin. *ACS Chem. Neurosci.* 4 (1), 48–63.
- Bandurin, D.A., Tyurnina, A.V., Yu, G.L., Mishchenko, A., Zólyomi, V., Morozov, S.V., Kumar, R.K., Gorbachev, R.V., Kudrynskiy, Z.R., Pezzini, S., 2017. High electron mobility, quantum Hall effect and anomalous optical response in atomically thin InSe. *Nat. Nanotechnol.* 12 (3), 223–227.
- Barbosa, Jr.F., Tanus-Santos, J.E., Gerlach, R.F., Parsons, P.J., 2005. A critical review of biomarkers used for monitoring human exposure to lead: advantages, limitations, and future needs. *Environ. Health Perspect.* 113 (12), 1669–1674.
- Barone, P.W., Baik, S., Heller, D.A., Strano, M.S., 2005a. Near-infrared optical sensors based on single-walled carbon nanotubes. *Nat. Mater.* 4 (1), 86–92.
- Barone, P.W., Parker, R.S., Strano, M.S., 2005b. In vivo fluorescence detection of glucose using a single-walled carbon nanotube optical sensor: design, fluorophore properties, advantages, and disadvantages. *Anal. Chem.* 77 (23), 7556–7562.
- Baughman, R.H., Zakhidov, A.A., De Heer, W.A., 2002. Carbon nanotubes—the route toward applications. *Science* 297 (5582), 787–792.
- Berger, M., Gray, J.A., Roth, B.L., 2009. The expanded biology of serotonin. *Annu. Rev. Med.* 60, 355–366.
- Berger, M., Gray, J.A., Roth, B.L., 2009a. The expanded biology of serotonin. *Annu. Rev. Med.* 60, 355–366.
- Berger, M., Gray, J.A., Roth, B.L., 2009b. The expanded biology of serotonin. *Annu. Rev. Med.* 60, 355.
- Berndt, T.J., Liang, M., Tyce, G.M., Knox, F.G., 2001. Intrarenal serotonin, dopamine, and phosphate handling in remnant kidneys. *Kidney Int.* 59 (2), 625–630.
- Blier, P., de Montigny, C., 1994. Current advances and trends in the treatment of depression. *Trends Pharmacol. Sci.* 15 (7), 220–226.
- Bortolato, M., Chen, K., Shih, J.C., 2010. The degradation of serotonin: role of MAO. *Handb. Behav. Neurobiol.* 21, 203–218.
- Bouatra, S., Aziat, F., Mandal, R., Guo, A.C., Wilson, M.R., Knox, C., Bjorn Dahl, T.C., Krishnamurthy, R., Saleem, F., Liu, P., 2013. The human urine metabolome. *PLoS One* 8 (9), e73076.
- Bowman, R.L., Caulfield, P.A., Udenfriend, S., 1955. Spectrophotofluorometric assay in the visible and ultraviolet. *Science* 122 (3157), 32–33.
- Brenner, B., Harney, J., Ahmed, B., Jeffus, B., Unal, R., Mehta, J., Kilic, F., 2007. Plasma serotonin levels and the platelet serotonin transporter. *J. Neurochem.* 102 (1), 206–215.
- Brustad, E.M., Lelyveld, V.S., Snow, C.D., Crook, N., Jung, S.T., Martinez, F.M., Scholl, T. J., Jasanoff, A., Arnold, F.H., 2012. Structure-guided directed evolution of highly selective P450-based magnetic resonance imaging sensors for dopamine and serotonin. *J. Mol. Biol.* 422 (2), 245–262.
- Cao, S., Zhou, L., Liu, C., Zhang, H., Zhao, Y., Zhao, Y., 2021. Pillararene-based self-assemblies for electrochemical biosensors. *Biosens. Bioelectron.* 181, 113164.
- Cardenas, C.G., Mar, L.P.D., Vysokanov, A.V., Arnold, P.B., Cardenas, L.M., Surmeier, D. J., Scroggs, R.S., 1999. Serotonergic modulation of hyperpolarization-activated current in acutely isolated rat dorsal root ganglion neurons. *J. Physiol.* 518 (2), 507–523.
- Cervenka, J., Budi, A., Dentschuk, N., Stacey, A., Tadich, A., Rietwyk, K.J., Schenk, A., Edmonds, M.T., Yin, Y., Medhekar, N., 2015. Graphene field effect transistor as a probe of electronic structure and charge transfer at organic molecule–graphene interfaces. *Nanoscale* 7 (4), 1471–1478.
- Cesarino, I., Galesco, H.V., Machado, S.A.S., 2014. Determination of serotonin on platinum electrode modified with carbon nanotubes/polypyrrole/silver nanoparticles nanohybrid. *Mater. Sci. Eng. C* 40, 49–54.
- Chandra, F., Dutta, T., Koner, A.L., 2020. Supramolecular encapsulation of a neurotransmitter serotonin by cucurbit [7] uril. *Front. Chem.* 8, 582757.
- Chang, C.-C., Li, C.-F., Yang, Z.-H., Lin, P.-Y., Chang, H.-C., Yang, C.-W., 2022. Target-induced recycling assembly of split aptamer fragments by DNA toehold-mediated displacement for the amplified colorimetric detection of estradiol. *Sensor. Actuator. B Chem.* 364, 131823.
- Chavan, S.G., Kim, D., Hwang, J., Choi, Y., Hong, J.W., Kim, J., Lee, M.H., Hwang, M.P., Choi, J., 2019a. Enhanced detection of infectious pancreatic necrosis virus via lateral flow chip and fluorometric biosensors based on self-assembled protein nanoprobe. *ACS Sens.* 4 (11), 2937–2944.
- Chavan, S.G., Rathod, P.R., Koyappayil, A., Go, A., Lee, M.-H., 2024. “Two-step” signal amplification for ultrasensitive detection of dopamine in human serum sample using Ti₃C₂Tx-MXene. *Sensor. Actuator. B Chem.* 404, 135308.
- Chavan, S.G., Yagati, A.K., Kim, H.T., Jin, E., Park, S.R., Patil, D.V., Lee, M.-H., 2021. Dimeric-serotonin bivalent ligands induced gold nanoparticle aggregation for highly sensitive and selective serotonin biosensor. *Biosens. Bioelectron.* 191, 113447.
- Chavan, S.G., Yagati, A.K., Koyappayil, A., Go, A., Yeon, S., Lee, M.-H., 2022a. Recombinant histidine-tagged nano-protein-based highly sensitive electro-sensing device for salivary cortisol. *Bioelectrochemistry* 144, 108046.
- Chavan, S.G., Yagati, A.K., Koyappayil, A., Go, A., Yeon, S., Lee, T., Lee, M.-H., 2022b. Conformationally flexible dimeric-serotonin-based sensitive and selective

- electrochemical biosensing strategy for serotonin recognition. *Anal. Chem.* 94 (49), 17020–17030.
- Chavan, S.G., Yagati, A.K., Mohammadniaei, M., Min, J., Lee, M.H., 2019b. Robust bioengineered apoferritin nanopores for ultrasensitive detection of infectious pancreatic necrosis virus. *Anal. Chem.* 91 (9), 5841–5849.
- Chávez, J.L., Hagen, J.A., Kelley-Loughnane, N., 2017a. Fast and selective plasmonic serotonin detection with aptamer-gold nanoparticle conjugates. *Sensors* 17 (4), 681.
- Chávez, J.L., Hagen, J.A., Kelley-Loughnane, N., 2017b. Fast and selective plasmonic serotonin detection with aptamer-gold nanoparticle conjugates. *Sensors*.
- Chen, J., Li, S., Chen, Y., Yang, J., Dong, J., Lu, X., 2021. L-Cysteine-Terminated triangular silver nanoplates/MXene nanosheets are used as electrochemical biosensors for efficiently detecting 5-hydroxytryptamine. *Anal. Chem.* 93 (49), 16655–16663.
- Chen, J.T., Shin, K., Leiston-Belanger, J.M., Zhang, M., Russell, T.P., 2006. Amorphous carbon nanotubes with tunable properties via template wetting. *Adv. Funct. Mater.* 16 (11), 1476–1480.
- Chhadva, P., Lee, T., Sarantopoulos, C.D., Hackam, A.S., McClellan, A.L., Felix, E.R., Levitt, R.C., Galor, A., 2015. Human tear serotonin levels correlate with symptoms and signs of dry eye. *Ophthalmology* 122 (8), 1675–1680.
- Cho, E.J., Lee, J.-W., Ellington, A.D., 2009. Applications of aptamers as sensors. *Annu. Rev. Anal. Chem.* 2, 241–264.
- Colowick, S.P., 1958. Arda alden green, protein chemist. *Science* 128 (3323), 519–521.
- Coyle, V.E., Brothers, M.C., McDonald, S., Kim, S.S., 2024. Superlative and selective sensing of serotonin in undiluted human serum using novel polystyrene sulfonate conductive polymer. *ACS Omega* 9 (14), 16800–16809.
- Dahlström, A., Fuxe, K., 1964. Localization of monoamines in the lower brain stem. *Experientia* 20 (7), 398–399.
- Dai, C., Liu, Y., Wei, D., 2022. Two-dimensional field-effect transistor sensors: the road toward commercialization. *Chem. Rev.* 122 (11), 10319–10392.
- De Volder, M.F., Tawfik, S.H., Baughman, R.H., Hart, A.J., 2013. Carbon nanotubes: present and future commercial applications. *Science* 339 (6119), 535–539.
- Dinarvand, M., Neubert, E., Meyer, D., Selvaggio, G., Mann, F.A., Erpenbeck, L., Kruss, S., 2019a. Near-infrared imaging of serotonin release from cells with fluorescent nanosensors. *Nano Lett.* 19 (9), 6604–6611.
- Dinarvand, M., Neubert, E., Meyer, D., Selvaggio, G., Mann, F.A., Erpenbeck, L., Kruss, S., 2019b. Near-infrared imaging of serotonin release from cells with fluorescent nanosensors. *Nano Lett.* 19 (9), 6604–6611.
- Doldán, X., Fagúndez, P., Cayota, A., Laíza, J., Tosar, J.P., 2016. Electrochemical sandwich immunosensor for determination of exosomes based on surface marker-mediated signal amplification. *Anal. Chem.* 88 (21), 10466–10473.
- Dong, Y., Zhang, L., 2022. Coupling surfactants with 3D hollow raspberry-like NiS/carbon microsphere with S vacancies for enhanced sensitivity monitoring of serotonin and L-tryptophan. *Sensor. Actuator. B Chem.* 368, 132140.
- Dresselhaus, G., Dresselhaus, M.S., Saito, R., 1998. Physical properties of carbon nanotubes. *World scientific*.
- Dresselhaus, M., Dresselhaus, G., Charlier, J.-C., Hernandez, E., 2004. Electronic, thermal and mechanical properties of carbon nanotubes. *Philos. Trans. R. Soc. London, Ser. A: Math. Phys. Eng. Sci.* 362 (1823), 2065–2098.
- Duerschmied, D., Suidan, G.L., Demers, M., Herr, N., Carbo, C., Brill, A., Cifuni, S.M., Mauler, M., Cicko, S., Bader, M., 2013. Platelet serotonin promotes the recruitment of neutrophils to sites of acute inflammation in mice. *Blood, The Journal of the American Society of Hematology* 121 (6), 1008–1015.
- Durham, E., Zhang, Y., LaRue, A., Bradshaw, A., Cray, J., 2020. Selective serotonin reuptake inhibitors (SSRI) affect murine bone lineage cells. *Life Sci.* 255, 117827.
- El-Merabhi, R., Löffler, M., Mayer, A., Sumara, G., 2015. The roles of peripheral serotonin in metabolic homeostasis. *FEBS (Fed. Eur. Biochem. Soc.) Lett.* 589 (15), 1728–1734.
- Ellington, A.D., Szostak, J.W., 1990. In vitro selection of RNA molecules that bind specific ligands. *Nature* 346 (6287), 818–822.
- Elnathan, R., Kwiatt, M., Pevzner, A., Engel, Y., Burstein, L., Khatchourians, A., Lichtenstein, A., Kantaev, R., Patolsky, F., 2012. Biorecognition layer engineering: overcoming screening limitations of nanowire-based FET devices. *Nano Lett.* 12 (10), 5245–5254.
- Ennaert, T., Schutyser, W., Dijkmans, J., Dusselier, M., Sels, B., 2016. Conversion of biomass to chemicals: the catalytic role of zeolites. *Zeolites and Zeolite-like Materials*. Elsevier, pp. 371–431.
- Erdbrügger, U., Blijdorp, C.J., Bijnstorp, I.V., Borràs, F.E., Burger, D., Bussolati, B., Byrd, J.B., Clayton, A., Dear, J.W., Falcón-Pérez, J.M., 2021. Urinary extracellular vesicles: a position paper by the urine task force of the international society for extracellular vesicles. *J. Extracell. Vesicles* 10 (7), e12093.
- Ersperer, V., Asero, B., 1952a. Identification of enteramine, the specific hormone of the enterochromaffin cell system, as 5-hydroxytryptamine. *Nature* 169, 800–801.
- Ersperer, V., Asero, B., 1952b. Identification of enteramine, the specific hormone of the enterochromaffin cell system, as 5-hydroxytryptamine. *Nature* 169 (4306), 800–801.
- Ersperer, V., Vialli, M., 1937. Ricerche sul secreto delle cellule enterocromaffini. *Boll. d Soc Med-chir Pavia* 51, 357–363.
- Escobar, L., Ballester, P., 2021. Molecular recognition in water using macrocyclic synthetic receptors. *Chem. Rev.* 121 (4), 2445–2514.
- Fagan-Murphy, A., Patel, B.A., 2014. Compressed multiwall carbon nanotube composite electrodes provide enhanced electroanalytical performance for determination of serotonin. *Electrochim. Acta* 138, 392–399.
- Falck, B., Hillarp, N.A., Thieme, G., Torp, A., 1982. Fluorescence of catechol amines and related compounds condensed with formaldehyde. *Brain Res. Bull.* 9 (1–6), xi–xv.
- Fan, R., Karnik, R., Yue, M., Li, D., Majumdar, A., Yang, P., 2005. DNA translocation in inorganic nanotubes. *Nano Lett.* 5 (9), 1633–1637.
- Farjami, E., Campos, R., Nielsen, J.S., Gothelf, K.V., Kjems, J., Ferapontova, E.E., 2013. RNA aptamer-based electrochemical biosensor for selective and label-free analysis of dopamine. *Anal. Chem.* 85 (1), 121–128.
- Fayemi, O.E., Adekunle, A.S., Ekenso, E.E., 2017. Electrochemical determination of serotonin in urine samples based on metal oxide nanoparticles/MWCNT on modified glassy carbon electrode. *Sensing and Bio-Sensing Research* 13, 17–27.
- Feng, J.-J., Guo, H., Li, Y.-F., Wang, Y.-H., Chen, W.-Y., Wang, A.-J., 2013. Single molecular functionalized gold nanoparticles for hydrogen-bonding recognition and colorimetric detection of dopamine with high sensitivity and selectivity. *ACS Appl. Mater. Interfaces* 5 (4), 1226–1231.
- Ferain, I., Colinge, C.A., Colinge, J.-P., 2011. Multigate transistors as the future of classical metal–oxide–semiconductor field-effect transistors. *Nature* 479 (7373), 310–316.
- Ferreira, J.N., Hoffman, M.P., 2013. Interactions between developing nerves and salivary glands. *Organogenesis* 9 (3), 199–205.
- Forsyth, R., Devadoss, A., Guy, O.J., 2017. Graphene field effect transistors for biomedical applications: current status and future prospects. *Diagnostics* 7 (3), 45.
- Fraer, M., Kilic, F., 2015. Serotonin: a different player in hypertension-associated thrombosis. *Hypertension* 65 (5), 942–948.
- Frutiger, A., Tanno, A., Hwu, S., Tiefenauer, R.F., Voros, J., Nakatsuka, N., 2021. Nonspecific binding—fundamental concepts and consequences for biosensing applications. *Chem. Rev.* 121 (13), 8095–8160.
- Fu, W., Jiang, L., van Geest, E.P., Lima, L.M., Schneider, G.F., 2017. Sensing at the surface of graphene field-effect transistors. *Adv. Mater.* 29 (6), 1603610.
- Gao, N., Gao, T., Yang, X., Dai, X., Zhou, W., Zhang, A., Lieber, C.M., 2016. Specific detection of biomolecules in physiological solutions using graphene transistor biosensors. *Proc. Natl. Acad. Sci. USA* 113 (51), 14633–14638.
- Gattuso, G., Notti, A., Pappalardo, S., Parisi, M.F., Pisagatti, I., Patanè, S., 2014. Encapsulation of monoamine neurotransmitters and trace amines by amphiphilic anionic calix [5] arene micelles. *New J. Chem.* 38 (12), 5983–5990.
- Ge, S., White, J.G., Haynes, C.L., 2009. Quantal release of serotonin from platelets. *Anal. Chem.* 81 (8), 2935–2943.
- Ge, S., Woo, E., White, J.G., Haynes, C.L., 2011. Electrochemical measurement of endogenous serotonin release from human blood platelets. *Anal. Chem.* 83 (7), 2598–2604.
- Geng, X., Zhang, M., Long, H., Hu, Z., Zhao, B., Feng, L., Du, J., 2021. A reusable neurotransmitter aptasensor for the sensitive detection of serotonin. *Anal. Chim. Acta* 1145, 124–131.
- Giachalone, F., Campisciano, V., Calabrese, C., La Parola, V., Syrgiannis, Z., Prato, M., Gruttadauria, M., 2016. Single-walled carbon nanotube–polyamidoamine dendrimer hybrids for heterogeneous catalysis. *ACS Nano* 10 (4), 4627–4636.
- Giamberardino, A., Labib, M., Hassan, E.M., Tetro, J.A., Springthorpe, S., Sattar, S.A., Berezovski, M.V., DeRosa, M.C., 2013. Ultrasensitive norovirus detection using DNA aptasensor technology. *PLoS One* 8 (11), e79087.
- Gibson, E.L., 2018. Tryptophan supplementation and serotonin function: genetic variations in behavioural effects. *Proc. Nutr. Soc.* 77 (2), 174–188.
- Goddard, J.-P., Raymond, J.-L., 2004. Enzyme assays for high-throughput screening. *Curr. Opin. Biotechnol.* 15 (4), 314–322.
- Godoy-Reyes, T.M., Costero, A.M., Gavina, P., Martínez-Máñez, R., Sancenón, F., 2019. A colorimetric probe for the selective detection of norepinephrine based on a double molecular recognition with functionalized gold nanoparticles. *ACS Appl. Nano Mater.* 2 (3), 1367–1373.
- Godoy-Reyes, T.M., Llopis-Lorente, A., Costero, A.M., Sancenón, F., Gavina, P., Martínez-Máñez, R., 2018a. Selective and sensitive colorimetric detection of the neurotransmitter serotonin based on the aggregation of bifunctionalised gold nanoparticles. *Sensor. Actuator. B Chem.* 258, 829–835.
- Godoy-Reyes, T.M., Llopis-Lorente, A., Costero, A.M., Sancenón, F., Gavina, P., Martínez-Máñez, R., 2018b. Selective and sensitive colorimetric detection of the neurotransmitter serotonin based on the aggregation of bifunctionalised gold nanoparticles. *Sensor. Actuator. B Chem.* 258, 829–835.
- Goyal, R.N., Agrawal, B., 2012. Ag ion irradiated based sensor for the electrochemical determination of epinephrine and 5-hydroxytryptamine in human biological fluids. *Anal. Chim. Acta* 743, 33–40.
- Goyal, R.N., Oyama, M., Gupta, V.K., Singh, S.P., Sharma, R.A., 2008. Sensors for 5-hydroxytryptamine and 5-hydroxyindole acetic acid based on nanomaterial modified electrodes. *Sensor. Actuator. B Chem.* 134 (2), 816–821.
- Greenwald, E.C., Mehta, S., Zhang, J., 2018. Genetically encoded fluorescent biosensors illuminate the spatiotemporal regulation of signaling networks. *Chem. Rev.* 118 (24), 11707–11794.
- Grenett, H.E., Ledley, F.D., Reed, L.L., Woo, S.L., 1987. Full-length cDNA for rabbit tryptophan hydroxylase: functional domains and evolution of aromatic amino acid hydroxylases. *Proc. Natl. Acad. Sci. U. S. A.* 84 (16), 5530–5534.
- Griessnauer, C.J., Chang, S.-Y., Tye, S.J., Kimble, C.J., Bennet, K.E., Garris, P.A., Lee, K. H., 2010. Wireless Instantaneous Neurotransmitter Concentration System: electrochemical monitoring of serotonin using fast-scan cyclic voltammetry—a proof-of-principle study. *J. Neurosurg.* 113 (3), 656–665.
- Grimm, L.M., Sinn, S., Krstić, M., D'Este, E., Sonntag, I., Prasetyanto, E.A., Kuner, T., Wenzel, W., De Cola, L., Biedermann, F., 2021. Fluorescent nanozeolite receptors for the highly selective and sensitive detection of neurotransmitters in water and biofluids. *Adv. Mater.* 33 (49), 2104614.
- Gupta, P., Goyal, R.N., 2014. Polymelamine modified edge plane pyrolytic graphite sensor for the electrochemical assay of serotonin. *Talanta* 120, 17–22.
- Han, J., Stine, J.M., Chapin, A.A., Ghodssi, R., 2023. A portable electrochemical sensing platform for serotonin detection based on surface-modified carbon fiber microelectrodes. *Anal. Methods* 15 (9), 1096–1104.

- Hart, J.L., Hantanasirisakul, K., Lang, A.C., Anasori, B., Pinto, D., Pivak, Y., van Omme, J. T., May, S.J., Gogotsi, Y., Taheri, M.L., 2019. Control of MXenes' electronic properties through termination and intercalation. *Nat. Commun.* 10 (1), 522.
- He, R., Tang, H., Jiang, D., Chen, H.-y., 2016. Electrochemical visualization of intracellular hydrogen peroxide at single cells. *Anal. Chem.* 88 (4), 2006–2009.
- Hedner, J., Lundell, K., Breeze, G., Mueller, R., Hedner, T., 1986. Developmental variations in CSF monoamine metabolites during childhood. *Neonatology* 49 (4), 190–197.
- Heiander, A., Beck, O., Boysen, L., 1995. 5-Hydroxytryptophol conjugation in man: influence of alcohol consumption and altered serotonin turnover. *Life Sci.* 56 (18), 1529–1534.
- Heins, E.A., Siwy, Z.S., Baker, L.A., Martin, C.R., 2005. Detecting single porphyrin molecules in a conically shaped synthetic nanopore. *Nano Lett.* 5 (9), 1824–1829.
- Heller, D.A., Jeng, E.S., Yeung, T.-K., Martinez, B.M., Moll, A.E., Gastala, J.B., Strano, M. S., 2006. Optical detection of DNA conformational polymorphism on single-walled carbon nanotubes. *Science* 311 (5760), 508–511.
- Heller, D.A., Jin, H., Martinez, B.M., Patel, D., Miller, B.M., Yeung, T.-K., Jena, P.V., Höbartner, C., Ha, T., Silverman, S.K., 2009. Multimodal optical sensing and analyte specificity using single-walled carbon nanotubes. *Nat. Nanotechnol.* 4 (2), 114–120.
- Heller, D.A., Pratt, G.W., Zhang, J., Nair, N., Hansborough, A.J., Boghossian, A.A., Reuel, N.F., Barone, P.W., Strano, M.S., 2011. Peptide secondary structure modulates single-walled carbon nanotube fluorescence as a chaperone sensor for nitroaromatics. *Proc. Natl. Acad. Sci. USA* 108 (21), 8544–8549.
- Hepel, M., Blake, D., McCabe, M., Stobiecka, M., Coopersmith, K., 2012. Assembly of gold nanoparticles induced by metal ions, Functional Nanoparticles for Bioanalysis. In: *Nanomedicine, and Bioelectronic Devices*, vol. 1. ACS Publications, pp. 207–240.
- Hoertel, N., Cipel, H., Blanco, C., Oquendo, M.A., Ellul, P., Leaute, E., Limosin, F., Peyre, H., Costemale-Lacoste, J.-F., 2021. Cerebrospinal fluid levels of monoamines among suicide attempters: a systematic review and random-effects meta-analysis. *J. Psychiatr. Res.* 136, 224–235.
- Hoffman, J.M., Gambhir, S.S., 2007. Molecular imaging: the vision and opportunity for radiology in the future. *Radiology* 244 (1), 39–47.
- Höglund, E., Øverli, Ø., Winberg, S., 2019. Tryptophan metabolic pathways and brain serotonergic activity: a comparative review. *Front. Endocrinol.* 10, 158.
- Holmes, J., Witt, C.E., Keen, D., Buchanan, A.M., Batey, L., Hersey, M., Hashemi, P., 2021. Glutamate electropolymerization on carbon increases analytical sensitivity to dopamine and serotonin: an auspicious in vivo phenomenon in mice? *Anal. Chem.* 93 (31), 10762–10771.
- Holmsen, H., Weiss, H.J., 1979. Secretory storage pools in platelets. *Annu. Rev. Med.* 30 (1), 119–134.
- Holt, J.K., Park, H.G., Wang, Y., Stadermann, M., Artyukhin, A.B., Grigoropoulos, C.P., Noy, A., Bakajin, O., 2006. Fast mass transport through sub-2-nanometer carbon nanotubes. *Science* 312 (5776), 1034–1037.
- Hong, G., Diao, S., Antaris, A.L., Dai, H., 2015. Carbon nanomaterials for biological imaging and nanomedicine. *Chem. Rev.* 115 (19), 10816–10906.
- Hsieh, V., Okada, S., Wei, H., Garcia-Alvarez, I., Barandov, A., Alvarado, S.R., Ohlendorf, R., Fan, J., Ortega, A., Jasanoff, A., 2019. Neurotransmitter-responsive nanosensors for T2-weighted magnetic resonance imaging. *J. Am. Chem. Soc.* 141 (40), 15751–15754.
- Huang, Y., Yin, S., Huang, Y., Zhang, X., Zhang, W., Jiang, G., Zhu, H., Wan, C., Fu, W., 2021. Graphene oxide/hexylamine superlattice field-effect biochemical sensors. *Adv. Funct. Mater.* 31 (23), 2010563.
- Huetner, G., Reimer, A., Schmidt, F., Schuff-Werner, P., Brudny, M., 1990. Oxidation of the indole nucleus of 5-hydroxytryptamine and formation of dimers in the presence of peroxidase and H₂O₂, Amine Oxidases and Their Impact on Neurobiology. *Proceedings of the 4 Th International Amine Oxidases Workshop*, Würzburg, Federal Republic of Germany, July 7–10, 1990. Springer, pp. 249–257.
- Iijima, S., 1991. Helical microtubules of graphitic carbon. *Nature* 354 (6348), 56–58.
- Iijima, S., Ichihashi, T., 1993. Single-shell carbon nanotubes of 1-nm diameter. *Nature* 363 (6430), 603–605.
- Im, H., AlMutairi, A., Kim, S., Sritharan, M., Kim, S., Yoon, Y., 2019. On MoS₂ thin-film transistor design consideration for a NO₂ gas sensor. *ACS Sens.* 4 (11), 2930–2936.
- Ip, I.-F., Wang, Y.-S., Chang, C.-C., 2023. Aptamer-based detection of serotonin based on the rapid in situ synthesis of colorimetric gold nanoparticles. *Nanotechnol. Rev.* 12 (1), 20220514.
- Israelachvili, J.N., 2011. *Intermolecular and Surface Forces*. Academic press.
- Jafri, S., Chandra, N., Dhawan, S., Soni, D., Chandra, M., Shanker, K., 1992. Factors influencing platelet serotonin uptake in essential hypertension. *Int. J. Cardiol.* 34 (3), 327–333.
- Jeng, E.S., Moll, A.E., Roy, A.C., Gastala, J.B., Strano, M.S., 2006. Detection of DNA hybridization using the near-infrared band-gap fluorescence of single-walled carbon nanotubes. *Nano Lett.* 6 (3), 371–375.
- Jeon, J., Yang, Y., Choi, H., Park, J.-H., Lee, B.H., Lee, S., 2020. MXenes for future nanophotonic device applications. *Nanophotonics* 9 (7), 1831–1853.
- Jeong, S., Yang, D., Beyene, A.G., Del Bonis-O'Donnell, J.T., Gest, A.M., Navarro, N., Sun, X., Landry, M.P., 2019. High-throughput evolution of near-infrared serotonin nanosensors. *Sci. Adv.* 5 (12), eaay3771.
- Jeong, S., Yang, D., Beyene, A.G., Del Bonis-O'Donnell, J.T., Gest, A.M.M., Navarro, N., Sun, X., Landry, M.P., 2019. High-throughput evolution of near-infrared serotonin nanosensors. *Sci. Adv.* 5(12), eaay3771.
- Jiang, M., Tian, L., Su, M., Cao, X., Jiang, Q., Huo, X., Yu, C., 2022. Real-time monitoring of 5-HT release from cells based on MXene hybrid single-walled carbon nanotubes modified electrode. *Anal. Bioanal. Chem.* 414 (28), 7967–7976.
- Johanson, C.E., Duncan, J.A., Klinge, P.M., Brinker, T., Stopa, E.G., Silverberg, G.D., 2008. Multiplicity of cerebrospinal fluid functions: new challenges in health and disease. *Cerebrospinal Fluid Res.* 5, 1–32.
- Julius, D., 1991. Molecular biology of serotonin receptors. *Annu. Rev. Neurosci.* 14 (1), 335–360.
- Junkaew, A., Arroyave, R., 2018. Enhancement of the selectivity of MXenes (M 2 C, M= Ti, V, Nb, Mo) via oxygen-functionalization: promising materials for gas-sensing and separation. *Phys. Chem. Chem. Phys.* 20 (9), 6073–6082.
- Karuppaiah, G., Lee, M.-H., Bhansali, S., Manickam, P., 2023. Electrochemical sensors for cortisol detection: principles, designs, fabrication, and characterisation. *Biosens. Bioelectron.* 239, 115600.
- Kelich, P., Jeong, S., Navarro, N., Adams, J., Sun, X., Zhao, H., Landry, M.P., Vuković, L., 2022. Discovery of DNA–carbon nanotube sensors for serotonin with machine learning and near-infrared fluorescence spectroscopy. *ACS Nano* 16 (1), 736–745.
- Kim, H., Toyofuku, Y., Lynn, F.C., Chak, E., Uchida, T., Mizukami, H., Fujitani, Y., Kawamori, R., Miyatsuka, T., Kosaka, Y., 2010. Serotonin regulates pancreatic beta cell mass during pregnancy. *Nat. Med.* 16 (7), 804–808.
- Kim, J.-H., Heller, D.A., Jin, H., Barone, P.W., Song, C., Zhang, J., Trudel, L.J., Wogan, G. N., Tannenbaum, S.R., Strano, M.S., 2009. The rational design of nitric oxide selectivity in single-walled carbon nanotube near-infrared fluorescence sensors for biological detection. *Nat. Chem.* 1 (6), 473–481.
- Kim, S.-K., Bae, S.-R., Ahmed, M.S., You, J.-M., Jeon, S.-W., 2011. Selective determination of serotonin on poly (3, 4-ethylenedioxy pyrrole)-single-walled carbon nanotube-modified glassy carbon electrodes. *Bull. Kor. Chem. Soc.* 32 (4), 1215–1220.
- Kim, S.K., Kim, D., Jeon, S., 2012. Electrochemical determination of serotonin on glassy carbon electrode modified with various graphene nanomaterials. *Sensor. Actuator. B Chem.* 174, 285–291.
- Kissinger, P.T., Hart, J.B., Adams, R.N., 1973. Voltammetry in brain tissue—a new neurophysiological measurement. *Brain Res.* 55 (1), 209–213.
- Kolesnichenko, I.V., Anslyn, E.V., 2017. Practical applications of supramolecular chemistry. *Chem. Soc. Rev.* 46 (9), 2385–2390.
- Kong, B., Zhu, A., Luo, Y., Tian, Y., Yu, Y., Shi, G., 2011. Sensitive and selective colorimetric visualization of cerebral dopamine based on double molecular recognition. *Angew. Chem.* 123 (8), 1877–1880.
- Konstantinou, G.N., 2017. Enzyme-linked immunosorbent assay (ELISA). *Food Allergens: Methods and Protocols* 79–94.
- Koyappayil, A., Chavan, S.G., Mohammadniaei, M., Go, A., Hwang, S.Y., Lee, M.-H., 2020. β -Hydroxybutyrate dehydrogenase decorated MXene nanosheets for the amperometric determination of β -hydroxybutyrate. *Microchim. Acta* 187, 1–7.
- Koyappayil, A., Chavan, S.G., Roh, Y.-G., Lee, M.-H., 2022. Advances of MXenes; perspectives on biomedical research. *Biosensors* 12 (7), 454.
- Krämer, J., Kang, R., Grimm, L.M., De Cola, L., Picchetti, P., Biedermann, F., 2022. Molecular probes, chemosensors, and nanosensors for optical detection of biorelevant molecules and ions in aqueous media and biofluids. *Chem. Rev.* 122 (3), 3459–3636.
- Krämer, U.M., Riba, J., Richter, S., Münte, T.F., 2011. An fMRI study on the role of serotonin in reactive aggression. *PLoS One* 6 (11), e27668.
- Kroeze, W.K., Kristiansen, K., Roth, B.L., 2002. Molecular biology of serotonin receptors: structure and function at the molecular level. *Curr. Top. Med. Chem.* 2 (6), 507–528.
- Kruss, S., Hilmer, A.J., Zhang, J., Reuel, N.F., Mu, B., Strano, M.S., 2013. Carbon nanotubes as optical biomedical sensors. *Adv. Drug Deliv. Rev.* 65 (15), 1933–1950.
- Kruss, S., Landry, M.P., Vander Ende, E., Lima, B.M.A., Reuel, N.F., Zhang, J., Nelson, J., Mu, B., Hilmer, A., Strano, M., 2014. Neurotransmitter detection using corona phase molecular recognition on fluorescent single-walled carbon nanotube sensors. *J. Am. Chem. Soc.* 136 (2), 713–724.
- Kumar, A., Purohit, B., Azad, U.P., Yarak, M.T., Dkhar, D.S., Tan, Y.N., Srivastava, A., Chandra, P., 2023. Gold nanostar and graphitic carbon nitride nanocomposite for serotonin detection in biological fluids and human embryonic kidney cell microenvironment. *Microchim. Acta* 190 (1), 45.
- Kumar, A.M., Kumar, M., Deepika, K., Fernandez, J.B., Eisdorfer, C., 1990. A modified HPLC technique for simultaneous measurement of 5-hydroxytryptamine and 5-hydroxyindoleacetic acid in cerebrospinal fluid, platelet and plasma. *Life Sci.* 47 (19), 1751–1759.
- Labib, M., Hedström, M., Amin, M., Mattiasson, B., 2009. A capacitive immunosensor for detection of cholera toxin. *Anal. Chim. Acta* 634 (2), 255–261.
- Labib, M., Zamay, A.S., Berezovski, M.V., 2013. Multifunctional electrochemical aptasensor for aptamer clones screening, virus quantitation in blood and viability assessment. *Analyst* 138 (6), 1865–1875.
- Lai, S., Vlamiadis, Y., Mishra, N., Cosseddu, P., Miskis, V., Ricci, P.C., Voliani, V., Coletti, C., Bonfiglio, A., 2021. A flexible, transparent chemosensor integrating an inkjet-printed organic field-effect transistor and a non-covalently functionalized graphene electrode. *Advanced Materials Technologies* 6 (12), 2100481.
- Lee, J., Kang, Y., Chang, J., Song, J., Kim, B.-K., 2020. Determination of serotonin concentration in single human platelets through single-entity electrochemistry. *ACS Sens.* 5 (7), 1943–1948.
- Lee, S., Xie, J., Chen, X., 2010. Peptide-based probes for targeted molecular imaging. *Biochemistry* 49 (7), 1364–1376.
- Lee, T., Cai, L.X., Lelyveld, V.S., Hai, A., Jasanoff, A., 2014. Molecular-level functional magnetic resonance imaging of dopaminergic signaling. *Science* 344 (6183), 533–535.
- Lee, Y.H., Jang, M., Lee, M.Y., Kwon, O.Y., Oh, J.H., 2017. Flexible field-effect transistor-type sensors based on conjugated molecules. *Chem* 3 (5), 724–763.
- Li, H.-Y., Huang, S.-Y., Zhou, D.-D., Xiong, R.-G., Luo, M., Saimaiti, A., Han, M.-K., Gan, R.-Y., Zhu, H.-L., Li, H.-B., 2023a. Theabrownin inhibits obesity and non-alcoholic fatty liver disease in mice via serotonin-related signaling pathways and gut-liver axis. *J. Adv. Res.*

- Li, H., Arroyo-Curras, N., Kang, D., Ricci, F., Plaxco, K.W., 2016a. Dual-reporter drift correction to enhance the performance of electrochemical aptamer-based sensors in whole blood. *J. Am. Chem. Soc.* 138 (49), 15809–15812.
- Li, J., Si, Y., Park, Y.E., Choi, J.-S., Jung, S.M., Lee, J.E., Lee, H.J., 2021. A serotonin voltammetric biosensor composed of carbon nanocomposites and DNA aptamer. *Microchim. Acta* 188, 1–8.
- Li, R., Li, X., Su, L., Qi, H., Yue, X., Qi, H., 2022. Label-free electrochemical aptasensor for the determination of serotonin. *Electroanalysis* 34 (6), 1048–1053.
- Li, S., Zhang, H., Zhu, M., Kuang, Z., Li, X., Xu, F., Miao, S., Zhang, Z., Lou, X., Li, H., Xia, F., 2023b. Electrochemical biosensors for whole blood analysis: recent progress, challenges, and future perspectives. *Chem. Rev.* 123 (12), 7953–8039.
- Li, Y.-T., Tang, L.-N., Ning, Y., Shu, Q., Liang, F.-X., Wang, H., Zhang, G.-J., 2016b. In vivo monitoring of serotonin by nanomaterial functionalized acupuncture needle. *Sci. Rep.* 6 (1), 28018.
- Lim, S.G., Seo, S.E., Park, S.J., Kim, J., Kim, Y., Kim, K.H., An, J.E., Kwon, O.S., 2022. Real-time monitoring of serotonin with highly selective aptamer-functionalized conducting polymer nanohybrids. *Nano Convergence* 9 (1), 31.
- Liscia, A., Solari, P., Gibbons, S.T., Gelperin, A., Stoffolano, J.G., 2012. Effect of serotonin and calcium on the supercontractile muscles of the adult blowfly crop. *J. Insect Physiol.* 58 (3), 356–366.
- Liu, R., Feng, Z.-Y., Li, D., Jin, B., Lan, Y., Meng, L.-Y., 2022. Recent trends in carbon-based microelectrodes as electrochemical sensors for neurotransmitter detection: a review. *TrAC, Trends Anal. Chem.* 148, 116541.
- Liu, X., He, F., Zhang, F., Zhang, Z., Huang, Z., Liu, J., 2020. Dopamine and melamine binding to gold nanoparticles dominates their aptamer-based label-free colorimetric sensing. *Anal. Chem.* 92 (13), 9370–9378.
- Liu, Y.-S., Yang, M., 2006. The effect of 5-hydroxytryptamine on the regulation of megakaryocytopoiesis. *Hematology* 11 (1), 53–56.
- Liu, Y., Li, M., Zhou, B., Xuan, X., Li, H., 2023. Flexible B, N co-doped graphene electrodes for electrochemical detection of serotonin in bodily fluids. *Electrochim. Acta* 457, 142494.
- Lubin, A.A., Plaxco, K.W., 2010. Folding-based electrochemical biosensors: the case for responsive nucleic acid architectures. *Accounts Chem. Res.* 43 (4), 496–505.
- Ludwig, C., Schmidt, A., 1868. *Arb. ad physiolog. Anstalt z. Leipzig* 3 (1).
- Maehashi, K., Katsura, T., Kerman, K., Takamura, Y., Matsumoto, K., Tamiya, E., 2007. Label-free protein biosensor based on aptamer-modified carbon nanotube field-effect transistors. *Anal. Chem.* 79 (2), 782–787.
- Mahmudi, G., Dangwal, S., Zarrintaj, P., Zhu, M., Mao, Y., McIlroy, D.N., Saeb, M.R., Vatanpour, V., Ramsey, J.D., Kim, S.-J., 2020a. NaA zeolite-coated meshes with tunable hydrophilicity for oil-water separation. *Separ. Purif. Technol.* 240, 116630.
- Mahmudi, G., Zarrintaj, P., Taghizadeh, A., Taghizadeh, M., Manouchehri, S., Dangwal, S., Ronte, A., Ganjali, M.R., Ramsey, J.D., Kim, S.-J., 2020b. From microporous to mesoporous mineral frameworks: an alliance between zeolite and chitosan. *Carbohydr. Res.* 489, 107930.
- Mammadova-Bach, E., Mauler, M., Braun, A., Duerschmied, D., 2018. Autocrine and paracrine regulatory functions of platelet serotonin. *Platelets* 29 (6), 541–548.
- Mann, J.J., Currier, D., Stanley, B., Oquendo, M.A., Amsel, L.V., Ellis, S.P., 2006. Can biological tests assist prediction of suicide in mood disorders? *Int. J. Neuropsychopharmacol.* 9 (4), 465–474.
- Mao, S., Chang, J., Pu, H., Lu, G., He, Q., Zhang, H., Chen, J., 2017. Two-dimensional nanomaterial-based field-effect transistors for chemical and biological sensing. *Chem. Soc. Rev.* 46 (22), 6872–6904.
- Martin, X., Brennan, M., 1994a. Serotonin in human tears. *Eur. J. Ophthalmol.* 4 (3), 159–165.
- Martin, X.D., Brennan, M.C., 1994b. Serotonin in human tears. *Eur. J. Ophthalmol.* 4 (3), 159–165.
- Martínez-Martínez, V., Arbeloa, F.L., 2020. *Dyes and Photoactive Molecules in Microporous Systems*. Springer.
- Matsunaga, M., Ishii, K., Ohtsubo, Y., Noguchi, Y., Ochi, M., Yamasue, H., 2017. Association between salivary serotonin and the social sharing of happiness. *PLoS One* 12 (7), e0180391.
- Mayer, M., Baeumner, A.J., 2019. A megatrend challenging analytical chemistry: biosensor and chemosensor concepts ready for the internet of things. *Chem. Rev.* 119 (13), 7996–8027.
- Mazloum-Ardakani, M., Khoshroo, A., 2014. High sensitive sensor based on functionalized carbon nanotube/ionic liquid nanocomposite for simultaneous determination of norepinephrine and serotonin. *J. Electroanal. Chem.* 717–718, 17–23.
- McNicol, A., Israels, S.J., 1999. Platelet dense granules: structure, function and implications for haemostasis. *Thromb. Res.* 95 (1), 1–18.
- Ménard-Moyon, C., Kostarelos, K., Prato, M., Bianco, A., 2010. Functionalized carbon nanotubes for probing and modulating molecular functions. *Chem. Biol.* 17 (2), 107–115.
- Meng, Z., Stolz, R.M., Mendecki, L., Mirica, K.A., 2019. Electrically-transduced chemical sensors based on two-dimensional nanomaterials. *Chem. Rev.* 119 (1), 478–598.
- Mercado, C.P., Kilic, F., 2010. Molecular mechanisms of SERT in platelets: regulation of plasma serotonin levels. *Mol. Interv.* 10 (4), 231.
- Mohammadniaei, M., Go, A., Chavan, S.G., Koyappayil, A., Kim, S.-E., Yoo, H.J., Min, J., Lee, M.-H., 2019. Relay-race RNA/barcode gold nanoflower hybrid for wide and sensitive detection of microRNA in total patient serum. *Biosens. Bioelectron.* 141, 111468.
- Moslah, M., Fredj, Z., Dridi, C., 2021. Development of a new highly sensitive serotonin sensor based on green synthesized silver nanoparticle decorated reduced graphene oxide. *Anal. Methods* 13 (43), 5187–5194.
- Mozaffari, S.A., Chang, T., Park, S.-M., 2010. Self-assembled monolayer as a pre-concentrating receptor for selective serotonin sensing. *Biosens. Bioelectron.* 26 (1), 74–79.
- Mufeeda, M., Ankitha, M., Rasheed, P.A., 2023. Nb₂CTx/Protonated carbon nitride nanocomposite for electrochemical detection of serotonin. *ACS Appl. Nano Mater.* 6 (22), 21152–21161.
- Nagatsu, T., 2004. Progress in monoamine oxidase (MAO) research in relation to genetic engineering. *Neurotoxicology* 25 (1), 11–20.
- Nair, J.A., Saisree, S., Aswathi, R., Sandhya, K., 2022. Ultra-selective and real-time detection of dopamine using molybdenum disulphide decorated graphene-based electrochemical biosensor. *Sensor. Actuator. B Chem.* 354, 131254.
- Nakatsuka, N., Faillétaz, A., Eggemann, D., Forró, C., Vörös, J., Momotenko, D., 2021. Aptamer conformational change enables serotonin biosensing with nanopipettes. *Anal. Chem.* 93 (8), 4033–4041.
- Nakatsuka, N., Yang, K.-A., Abendroth, J.M., Cheung, K.M., Xu, X., Yang, H., Zhao, C., Zhu, B., Rim, Y.S., Yang, Y., 2018a. Aptamer-field-effect transistors overcome Debye length limitations for small-molecule sensing. *Science* 362 (6412), 319–324.
- Nakatsuka, N., Yang, K.A., Abendroth, J.M., Cheung, K.M., Xu, X., Yang, H., Zhao, C., Zhu, B., Rim, Y.S., Yang, Y., Weiss, P.S., Stojanović, M.N., Andrews, A.M., 2018b. Aptamer-field-effect transistors overcome Debye length limitations for small-molecule sensing. *Science* 362 (6412), 319–324.
- Nichols, D.E., Nichols, C.D., 2008. Serotonin receptors. *Chem. Rev.* 108 (5), 1614–1641.
- Nicholson, R.S., Shain, I., 1965. Theory of stationary electrode polarography for a chemical reaction coupled between two charge transfers. *Anal. Chem.* 37 (2), 178–190.
- Nilam, M., Karmacharya, S., Nau, W.M., Hennig, A., 2022. Proton-gradient-driven sensitivity enhancement of liposome-encapsulated supramolecular chemosensors. *Angew. Chem. Int. Ed.* 61 (35), e202207950.
- Nishitani, S., Man, Y., Noguchi, T., Sakata, T., 2022. Polyaniline-based nanostructure interface for signal-to-noise ratio enhancement in potentiometric enzyme-free biosensors. *Adv. Mater. Interfac.* 9 (27), 2201029.
- Nishitani, S., Sakata, T., 2020. Enhancement of signal-to-noise ratio for serotonin detection with well-designed nanofilter-coated potentiometric electrochemical biosensor. *ACS Appl. Mater. Interfaces* 12 (13), 14761–14769.
- Nishizawa, S., Benkelfat, C., Young, S.N., Leyton, M., Mzengeza, S., de Montigny, C., Blier, P., Diksik, M., 1997. Differences between males and females in rates of serotonin synthesis in human brain. *Proc. Natl. Acad. Sci. U. S. A.* 94 (10), 5308–5313.
- Noda, M., Higashida, H., Aoki, S., Wada, K., 2004. Multiple signal transduction pathways mediated by 5-HT receptors. *Mol. Neurobiol.* 29 (1), 31–39.
- Novak, S.J., 1997. LSD before Leary: sidney Cohen's critique of 1950s psychedelic drug research. *Isis* 88 (1), 87–110.
- O'connell, M.J., Bachilo, S.M., Huffman, C.B., Moore, V.C., Strano, M.S., Haroz, E.H., Rialon, K.L., Boul, P.J., Noon, W.H., Kittrell, C., 2002. Band gap fluorescence from individual single-walled carbon nanotubes. *Science* 297 (5581), 593–596.
- Ogston, D., 2012. *The Physiology of Hemostasis*. Springer Science & Business Media.
- Pandey, G.N., 1997. Altered serotonin function in suicide: evidence from platelet and neuroendocrine studies. *Ann. N. Y. Acad. Sci.* 836 (1), 182–201.
- Panneer Selvam, S., Yun, K., 2020. A self-assembled silver chalcogenide electrochemical sensor based on rGO-Ag₂Se for highly selective detection of serotonin. *Sensor. Actuator. B Chem.* 302, 127161.
- Peaston, R.T., Weinkove, C., 2004. Measurement of catecholamines and their metabolites. *Ann. Clin. Biochem.* 41 (1), 17–38.
- Peigney, A., Laurent, C., Flahaut, E., Bacsa, R., Rousset, A., 2001. Specific surface area of carbon nanotubes and bundles of carbon nanotubes. *Carbon* 39 (4), 507–514.
- Pourhamzeh, M., Moravej, F.G., Arabi, M., Shahriari, E., Mehrabi, S., Ward, R., Ahadi, R., Joghataei, M.T., 2021. The roles of serotonin in neuropsychiatric disorders. *Cell. Mol. Neurobiol.* 1–22.
- Pourhamzeh, M., Moravej, F.G., Arabi, M., Shahriari, E., Mehrabi, S., Ward, R., Ahadi, R., Joghataei, M.T., 2022. The roles of serotonin in neuropsychiatric disorders. *Cell. Mol. Neurobiol.* 42 (6), 1671–1692.
- Prato, M., Kostarelos, K., Bianco, A., 2008. Functionalized carbon nanotubes in drug design and discovery. *Accounts Chem. Res.* 41 (1), 60–68.
- Pu, K., Shuhendler, A.J., Jokerst, J.V., Mei, J., Gambhir, S.S., Bao, Z., Rao, J., 2014. Semiconducting polymer nanoparticles as photoacoustic molecular imaging probes in living mice. *Nat. Nanotechnol.* 9 (3), 233–239.
- Ran, G., Chen, X., Xia, Y., 2017. Electrochemical detection of serotonin based on a poly (bromocresol green) film and Fe₃O₄ nanoparticles in a chitosan matrix. *RSC Adv.* 7 (4), 1847–1851.
- Ran, G., Xia, Y., Liang, L., Fu, C., 2021. Enhanced response of sensor on serotonin using nickel-reduced graphene oxide by atomic layer deposition. *Bioelectrochemistry* 140, 107820.
- Rao, M., Gershon, M.D., 2018. Enteric nervous system development: what could possibly go wrong? *Nat. Rev. Neurosci.* 19 (9), 552–565.
- Rapport, M.M., Green, A., Page, I.H., 1949. Serum vasoconstrictor (serotonin). *J. Biol. Chem.* 176, 1243–1251.
- Rapport, M.M., Green, A.A., Page, I.H., 1948a. Partial purification of the vasoconstrictor in beef serum. *J. Biol. Chem.* 174 (2), 735–741.
- Rapport, M.M., Green, A.A., Page, I.H., 1948b. Serum vasoconstrictor (serotonin): IV. Isolation and characterization. *J. Biol. Chem.* 176 (3), 1243–1251.
- Rathnakumar, K., Ramachandran, K., Baba, D., Ramesh, V., Vidhya, R., Vinothkumar, R., Poovitha, R., Geetha, R., 2018. Prevalence of dry eye disease and its association with dyslipidemia. *J. Basic Clin. Physiol. Pharmacol.* 29 (2), 195–199.
- Reuel, N.F., Grassbaugh, B., Kruss, S., Mundy, J.Z., Opel, C., Oggunniyi, A.O., Egodage, K., Wahl, R., Helk, B., Zhang, J., 2013. Emergent properties of nanosensor arrays: applications for monitoring IgG affinity distributions, weakly affinity

- hypermannosylation, and colony selection for biomanufacturing. *ACS Nano* 7 (9), 7472–7482.
- Robinson, D.L., Hermans, A., Seipel, A.T., Wightman, R.M., 2008. Monitoring rapid chemical communication in the brain. *Chem. Rev.* 108 (7), 2554–2584.
- Rodríguez, M.J., Saura, J., Billett, E.E., Finch, C.C., Mahy, N., 2001. Cellular localization of monoamine oxidase A and B in human tissues outside of the central nervous system. *Cell Tissue Res.* 304, 215–220.
- Ronkainen, N.J., Halsall, H.B., Heineman, W.R., 2010. Electrochemical biosensors. *Chem. Soc. Rev.* 39 (5), 1747–1763.
- Roth, B.L., Xia, Z., 2004. Molecular and cellular mechanisms for the polarized sorting of serotonin receptors: relevance for genesis and treatment of psychosis. *Crit. Rev. Neurobiol.* 16 (4).
- Sainio, E.-L., Pulkki, K., Young, S., 1996. L-Tryptophan: biochemical, nutritional and pharmacological aspects. *Amino Acids* 10, 21–47.
- Sakka, L., Coll, G., Chazal, J., 2011. Anatomy and physiology of cerebrospinal fluid. *European Annals of Otorhinolaryngology, Head and Neck Diseases* 128 (6), 309–316.
- Samie, H.A., Arvand, M., 2019. RuO₂ nanowires on electrospun CeO₂-Au nanofibers/functionalized carbon nanotubes/graphite oxide nanocomposite modified screen-printed carbon electrode for simultaneous determination of serotonin, dopamine and ascorbic acid. *J. Alloys Compd.* 782, 824–836.
- Santos-Cancel, M., Simpson, L.W., Leach, J.B., White, R.J., 2019. Direct, real-time detection of adenosine triphosphate release from astrocytes in three-dimensional culture using an integrated electrochemical aptamer-based sensor. *ACS Chem. Neurosci.* 10 (4), 2070–2079.
- Satishkumar, B., Brown, L.O., Gao, Y., Wang, C.-C., Wang, H.-L., Doorn, S.K., 2007. Reversible fluorescence quenching in carbon nanotubes for biomolecular sensing. *Nat. Nanotechnol.* 2 (9), 560–564.
- Schöning, M.J., Poghosian, A., 2002. Recent advances in biologically sensitive field-effect transistors (BioFETs). *Analyst* 127 (9), 1137–1151.
- Schroeder, V., Savagatrup, S., He, M., Lin, S., Swager, T.M., 2019. Carbon nanotube chemical sensors. *Chem. Rev.* 119 (1), 599–663.
- Selvarajan, S., Suganthi, A., Rajarajan, M., 2018. A novel highly selective and sensitive detection of serotonin based on Ag/polypyrrole/Cu₂O nanocomposite modified glassy carbon electrode. *Ultrason. Sonochem.* 44, 319–330.
- Selvaraju, T., Ramaraj, R., 2003. Simultaneous determination of ascorbic acid, dopamine and serotonin at poly (phenosafranin) modified electrode. *Electrochem. Commun.* 5 (8), 667–672.
- Seo, G., Lee, G., Kim, M.J., Baek, S.-H., Choi, M., Ku, K.B., Lee, C.-S., Jun, S., Park, D., Kim, H.G., Kim, S.-J., Lee, J.-O., Kim, B.T., Park, E.C., Kim, S.I., 2020. Rapid detection of COVID-19 causative virus (SARS-CoV-2) in human nasopharyngeal swab specimens using field-effect transistor-based biosensor. *ACS Nano* 14 (4), 5135–5142.
- Service, R.F., 2005. How far can we Push chemical self-assembly? *Science* 309 (5731), 95, 95.
- Sha, Q., Sun, B., Yi, C., Guan, R., Fei, J., Hu, Z., Liu, B., Liu, X., 2019. A fluorescence turn-on biosensor based on transferrin encapsulated gold nanoclusters for 5-hydroxytryptamine detection. *Sensor. Actuator. B Chem.* 294, 177–184.
- Shahid, M.M., Rameshkumar, P., Numan, A., Shahabuddin, S., Alizadeh, M., Khiew, P.S., Chiu, W.S., 2019. A cobalt oxide nanocubes interleaved reduced graphene oxide nanocomposite modified glassy carbon electrode for amperometric detection of serotonin. *Mater. Sci. Eng. C* 100, 388–395.
- Shapiro, M.G., Westmeyer, A.G., Romero, P.A., Szabolowski, J.O., Küster, B., Shah, A., Otey, C.R., Langer, R., Arnold, F.H., Jasanoff, A., 2010. Directed evolution of a magnetic resonance imaging contrast agent for noninvasive imaging of dopamine. *Nat. Biotechnol.* 28 (3), 264–270.
- Sharma, S., Singh, N., Tomar, V., Chandra, R., 2018. A review on electrochemical detection of serotonin based on surface modified electrodes. *Biosens. Bioelectron.* 107, 76–93.
- Shekher, K., Sampath, K., Vandini, S., Satyanarayana, M., Gobi, K.V., 2023. Gold nanoparticle assimilated polymer layer on carbon nanotube matrices for sensitive detection of serotonin in presence of dopamine in-vitro. *Inorg. Chim. Acta.* 549, 121399.
- Sinha, K., Chakraborty, A., Ahmed, Z., Mukherjee, P., Dutta, P., Das Mukhopadhyay, C., RoyChaudhuri, C., 2023. Molecularly imprinted polymer interface on screen-printed ZnO nanorod field effect transistors for serotonin detection in clinical samples. *ACS Biomater. Sci. Eng.* 9 (10), 5886–5899.
- Sinha, K., Chakraborty, B., Chaudhury, S.S., Chaudhuri, C.R., Chattopadhyay, S., Mukhopadhyay, C.D., 2021. Selective, ultra-sensitive, and rapid detection of serotonin by optimized ZnO nanorod FET biosensor. *IEEE Trans. NanoBioscience* 21 (1), 65–74.
- Some, M., Helander, A., 2002. Urinary excretion patterns of 5-hydroxyindole-3-acetic acid and 5-hydroxytryptophol in various animal species: implications for studies on serotonin metabolism and turnover rate. *Life Sci.* 71 (20), 2341–2349.
- Song, G., Zou, Z., Feng, A., Li, C., Liang, M., Wang, F., Liu, X., 2023. Light-up aptameric sensor of serotonin for point-of-care use. *Anal. Chem.* 95 (23), 9076–9082.
- Soslau, G., 2022. Cardiovascular serotonergic system: evolution, receptors, transporter, and function. *J. Exp. Zool. Part A: Ecological and Integrative Physiology* 337 (2), 115–127.
- Steckl, A.J., Ray, P., 2018. Stress biomarkers in biological fluids and their point-of-use detection. *ACS Sens.* 3 (10), 2025–2044.
- Stern, E., Wagner, R., Sigworth, F.J., Breaker, R., Fahmy, T.M., Reed, M.A., 2007. Importance of the Debye screening length on nanowire field effect transistor sensors. *Nano Lett.* 7 (11), 3405–3409.
- Stoll, W.A., 1947. Lysergsäure-diäthylamid, ein Phantastikum aus der Mutterkorngruppe. Royal Society of Medicine. Microfilm unit.
- Stunes, A., Reseland, J.E., Hauso, Ø., Kidd, M., Tømmerås, K., Waldum, H., Syversen, U., Gustafsson, B., 2011. Adipocytes express a functional system for serotonin synthesis, reuptake and receptor activation. *Diabetes Obes. Metabol.* 13 (6), 551–558.
- Su, D.S., Perathoner, S., Centi, G., 2013. Nanocarbons for the development of advanced catalysts. *Chem. Rev.* 113 (8), 5782–5816.
- Su, M., Lan, H., Tian, L., Jiang, M., Cao, X., Zhu, C., Yu, C., 2022. Ti3C₂Tx-reduced graphene oxide nanocomposite-based electrochemical sensor for serotonin in human biofluids. *Sensor. Actuator. B Chem.* 367, 132019.
- Sun, D., Li, H., Li, M., Li, C., Dai, H., Sun, D., Yang, B., 2018. Electrodeposition synthesis of a NiO/CNT/PEDOT composite for simultaneous detection of dopamine, serotonin, and tryptophan. *Sensor. Actuator. B Chem.* 259, 433–442.
- Sun, Y., Fei, J., Hou, J., Zhang, Q., Liu, Y., Hu, B., 2009. Simultaneous determination of dopamine and serotonin using a carbon nanotubes-ionic liquid gel modified glassy carbon electrode. *Microchim. Acta* 165, 373–379.
- Swensen, J.S., Xiao, Y., Ferguson, B.S., Lubin, A.A., Lai, R.Y., Heeger, A.J., Plaxco, K.W., Soh, H.T., 2009. Continuous, real-time monitoring of cocaine in undiluted blood serum via a microfluidic, electrochemical aptamer-based sensor. *J. Am. Chem. Soc.* 131 (12), 4262–4266.
- Szewczyk, A.K., Ulutas, S., Aktürk, T., Al-Hassany, L., Börner, C., Cernigliaro, F., Kodounis, M., Lo Cascio, S., Mikolajek, D., Onan, D., 2023. Prolactin and oxytocin: potential targets for migraine treatment. *J. Headache Pain* 24 (1), 31.
- Tan, Z.-L., Bao, A.-M., Tao, M., Liu, Y.-J., Zhou, J.-N., 2007. Circadian rhythm of salivary serotonin in patients with major depressive disorder. *Neuroendocrinol. Lett.* 28 (4), 395–400.
- Tang, Q., Zhou, Z., Shen, P., 2012. Are MXenes promising anode materials for Li ion batteries? Computational studies on electronic properties and Li storage capability of Ti₃C₂ and Ti₃C₂X₂ (X = F, OH) monolayer. *J. Am. Chem. Soc.* 134 (40), 16909–16916.
- Tang, S., Liang, A., Liu, M., Wang, W., Zhang, F., Luo, A., 2023. A glassy carbon electrode modified with a composite consisting of electrodeposited chitosan and carboxylated multi-walled carbon nanotubes for simultaneous voltammetric determination of dopamine, serotonin and melatonin. *Carbon Letters* 1–11.
- Tertiş, M., Cernat, A., Lacatiş, D., Florea, A., Bogdan, D., Suciuc, M., Săndulescu, R., Cristea, C., 2017. Highly selective electrochemical detection of serotonin on polypyrrole and gold nanoparticles-based 3D architecture. *Electrochem. Commun.* 75, 43–47.
- Tessonier, J.P., Becker, M., Xia, W., Girgsdies, F., Blume, R., Yao, L., Su, D.S., Muhler, M., Schlögl, R., 2010. Spinel-type cobalt-manganese-based mixed oxide as sacrificial catalyst for the high-yield production of homogeneous carbon nanotubes. *ChemCatChem* 2 (12), 1559–1561.
- Thanh, T.D., Balamurugan, J., Hien, H.V., Kim, N.H., Lee, J.H., 2017. A novel sensitive sensor for serotonin based on high-quality of AuAg nanoalloy encapsulated graphene electrocatalyst. *Biosens. Bioelectron.* 96, 186–193.
- Trabado, S., Al-Salameh, A., Croixmarie, V., Masson, P., Corruble, E., Fève, B., Colle, R., Ripoll, L., Walther, B., Boursier-Neyret, C., 2017. The human plasma-metabolome: reference values in 800 French healthy volunteers; impact of cholesterol, gender and age. *PLoS One* 12 (3), e0173615.
- Tran, B.N., Pham, H.T., Tran, B.N., Vu, D.-T., Do, H.H., Pham, M.T.N., Nguyen, H.T.A., Pham, B., 2024. Minimizing false positives in gold nanoparticle–aptamer biosensors for enhanced serotonin detection. *ACS Appl. Nano Mater.* 7 (15), 17697–17706.
- Tuerk, C., Gold, L., 1990. Systematic evolution of ligands by exponential enrichment: RNA ligands to bacteriophage T4 DNA polymerase. *Science* 249 (4968), 505–510.
- Turner, A., Pilitsky, S., 2005. Biosensors and Biomimetic Sensors for the Detection of Drugs, Toxins and Biological Agents, Defense against Bioterror. Springer, pp. 261–272.
- Twarog, B.M., Page, I.H., 1953a. Serotonin content of some mammalian tissues and urine and a method for its determination. *American Journal of Physiology-Legacy Content* 175 (1), 157–161.
- Twarog, B.M., Page, I.H., 1953b. Serotonin content of some mammalian tissues and urine and a method for its determination. *Am. J. Physiol.* 175 (1), 157–161.
- Tyagi, D., Wang, H., Huang, W., Hu, L., Tang, Y., Guo, Z., Ouyang, Z., Zhang, H., 2020. Recent advances in two-dimensional-material-based sensing technology toward health and environmental monitoring applications. *Nanoscale* 12 (6), 3535–3559.
- VahidMohammadi, A., Rosen, J., Gogotsi, Y., 2021. The world of two-dimensional carbides and nitrides (MXenes). *Science* 372 (6547), eabf1581.
- Vašček, O., Lojek, A., Číž, M., 2020. Serotonin and its metabolites reduce oxidative stress in murine RAW264. 7 macrophages and prevent inflammation. *J. Physiol. Biochem.* 76 (1), 49–60.
- Veening, J.G., Barendregt, H.P., 2010. The regulation of brain states by neuroactive substances distributed via the cerebrospinal fluid; a review. *Cerebrospinal Fluid Res.* 7 (1), 1–16.
- Veeralingam, S., Badhulika, S., 2020a. Biconcave Bi₂WO₆ nanoparticles for UV light-activated detection of nicotine in human sweat and cigarette samples. *ACS Appl. Nano Mater.* 3 (12), 12250–12259.
- Veeralingam, S., Badhulika, S., 2020b. Surface functionalized β-Bi₂O₃ nanofibers based flexible, field-effect transistor-biosensor (BioFET) for rapid, label-free detection of serotonin in biological fluids. *Sensor. Actuator. B Chem.* 321, 128540.
- Venkatesan, M., Vusa, C.S.R., Koyappayil, A., Chavan, S.G., Lee, M.-H., 2024. Biological recognition element anchored 2D graphene materials for the electrochemical detection of hazardous pollutants. *Electrochim. Acta* 494, 144413.
- Vigh, B., Manzano de Silva, M.J., et al., 2005. The system of cerebrospinal fluid contacting neurons in *Xenopus laevis*. *Ann NY Acad Sci* 1040, 249–252.
- Virkkunen, M., Goldman, D., Nielsen, D.A., Linnoila, M., 1995. Low brain serotonin turnover rate (low CSF 5-HIAA) and impulsive violence. *J. Psychiatr. Neurosci.* 20 (4), 271.

- Virkkunen, M., Linnoila, M., 1990. Serotonin in early onset, male alcoholics with violent behaviour. *Ann. Med.* 22 (5), 327–331.
- Walther, D.J., Peter, J.U., Bashammakh, S., Hörtnagl, H., Voits, M., Fink, H., Bader, M., 2003. Synthesis of serotonin by a second tryptophan hydroxylase isoform. *Science* 299 (5603), 76.
- Wan, Y., Zhou, Y.G., Poudineh, M., Safaei, T.S., Mohamadi, R.M., Sargent, E.H., Kelley, S. O., 2014. Highly specific electrochemical analysis of cancer cells using multi-nanoparticle labeling. *Angew. Chem.* 126 (48), 13361–13365.
- Wang, H., Li, H., Huang, Y., Xiong, M., Wang, F., Li, C., 2019. A label-free electrochemical biosensor for highly sensitive detection of gliotoxin based on DNA nanostructure/MXene nanocomplexes. *Biosens. Bioelectron.* 142, 111531.
- Wang, S., Wang, Y., Min, Q., Shu, T., Zhu, X., Peng, A., Ding, H., 2016. Simultaneous electrochemical determination of dopamine and serotonin in rat cerebrospinal fluid using screen-printed electrode modified with MWNTs-SiO₂-chitosan composites. *Int. J. Electrochem. Sci.* 11, 2360–2376.
- Wang, W., Zhang, B., Zhang, Y., Ma, P., Wang, X., Sun, Y., Song, D., Fei, Q., 2021. Colorimetry and SERS dual-mode sensing of serotonin based on functionalized gold nanoparticles. *Spectrochim. Acta Mol. Biomol. Spectrosc.* 261, 120057.
- Wang, Z.-h., Liang, Q.-l., Wang, Y.-m., Luo, G.-a., 2003. Carbon nanotube-intercalated graphite electrodes for simultaneous determination of dopamine and serotonin in the presence of ascorbic acid. *J. Electroanal. Chem.* 540, 129–134.
- Wang, Z., Zhang, Y., Zhang, B., Lu, X., 2018. Mn²⁺ doped ZnS QDs modified fluorescence sensor based on molecularly imprinted polymer/sol-gel chemistry for detection of Serotonin. *Talanta* 190, 1–8.
- Wei, H., Frey, A.M., Jasanoff, A., 2021. Molecular fMRI of neurochemical signaling. *J. Neurosci. Methods* 364, 109372.
- Weissman, M.M., Olfson, M., 1995. Depression in women: implications for health care research. *Science* 269 (5225), 799–801.
- Whitaker-Azmitia, P.M., 1999. The discovery of serotonin and its role in neuroscience. *Neuropsychopharmacology* 21 (1), 2–8.
- Woittiez, A., Wonting, G., Man't Veld, A., Boomsma, F., Schalekamp, M., 1985. Ketanserin: a possible tool for studying the role of serotonin in hypertension. *J. Cardiovasc. Pharmacol.* 7, 130–136.
- Woolley, D.W., Shaw, E., 1954. A biochemical and pharmacological suggestion about certain mental disorders. *Proc. Natl. Acad. Sci. U. S. A.* 40 (4), 228–231.
- Wrona, M.Z., Dryhurst, G., 1991. Interactions of 5-hydroxytryptamine with oxidative enzymes. *Biochem. Pharmacol.* 41 (8), 1145–1162.
- Wu, B., Yeasmin, S., Liu, Y., Cheng, L.-J., 2022. Sensitive and selective electrochemical sensor for serotonin detection based on ferrocene-gold nanoparticles decorated multiwall carbon nanotubes. *Sensor. Actuator. B Chem.* 354, 131216.
- Wu, K., Fei, J., Hu, S., 2003. Simultaneous determination of dopamine and serotonin on a glassy carbon electrode coated with a film of carbon nanotubes. *Anal. Biochem.* 318 (1), 100–106.
- Xia, F., Wang, H., Xiao, D., Dubey, M., Ramasubramaniam, A., 2014. Two-dimensional material nanophotonics. *Nat. Photonics* 8 (12), 899–907.
- Xiao, Y., Piorek, B.D., Plaxco, K.W., Heeger, A.J., 2005. A reagentless signal-on architecture for electronic, aptamer-based sensors via target-induced strand displacement. *J. Am. Chem. Soc.* 127 (51), 17990–17991.
- Xie, Y., Kent, P., 2013. Hybrid density functional study of structural and electronic properties of functionalized Ti n+ 1 X n (X= C, N) monolayers. *Phys. Rev. B* 87 (23), 235441.
- Xu, Z., Zhao, Y., 2023. 19F-Labeled probes for recognition-enabled chromatographic 19F NMR. *Chem. Rec.*, e202300031.
- Yagati, A.K., Wu, T., Chavan, S.G., Lee, M.-K., Lee, M.-H., Min, J., 2023. DNA aptamers on borophene nanosheets as an electrochemical system for omicron detection. *ACS Appl. Nano Mater.*
- Yang, M., Wang, L., Lu, H., Dong, Q., 2023. Advances in MXene-based electrochemical (bio) sensors for neurotransmitter detection. *Micromachines* 14 (5), 1088.
- Yazdi, M.K., Zarrintaj, P., Hosseiniamolli, H., Mashhadzadeh, A.H., Saeb, M.R., Ramsey, J.D., Ganjali, M.R., Mozafari, M., 2020. Zeolites for theranostic applications. *J. Mater. Chem. B* 8 (28), 5992–6012.
- Yildiz, O., Smith, J., Purdy, R., 1998. Serotonin and vasoconstrictor synergism. *Life Sci.* 62 (19), 1723–1732.
- Yola, M.L., Atar, N., 2018. A novel detection approach for serotonin by graphene quantum dots/two-dimensional (2D) hexagonal boron nitride nanosheets with molecularly imprinted polymer. *Appl. Surf. Sci.* 458, 648–655.
- Zen, J.-M., Chen, I.-L., Shih, Y., 1998. Voltammetric determination of serotonin in human blood using a chemically modified electrode. *Anal. Chim. Acta* 369 (1–2), 103–108.
- Zervas, N.T., Liszczak, T.M., Mayberg, M.R., Black, P.M., 1982. Cerebrospinal fluid may nourish cerebral vessels through pathways in the adventitia that may be analogous to systemic vasa vasorum. *J. Neurosurg.* 56 (4), 475–481.
- Zhang, J., Boghossian, A.A., Barone, P.W., Rwei, A., Kim, J.-H., Lin, D., Heller, D.A., Hilmer, A.J., Nair, N., Reuel, N.F., 2011. Single molecule detection of nitric oxide enabled by d (AT) 15 DNA adsorbed to near infrared fluorescent single-walled carbon nanotubes. *J. Am. Chem. Soc.* 133 (3), 567–581.
- Zhang, R., Liu, J., Li, Y., 2019. MXene with great adsorption ability toward organic dye: an excellent material for constructing a ratiometric electrochemical sensing platform. *ACS Sens.* 4 (8), 2058–2064.
- Zhang, S., Geryak, R., Geldmeier, J., Kim, S., Tsukruk, V.V., 2017. Synthesis, assembly, and applications of hybrid nanostructures for biosensing. *Chem. Rev.* 117 (20), 12942–13038.
- Zhao, C., Cheung, K.M., Huang, I.-W., Yang, H., Nakatsuka, N., Liu, W., Cao, Y., Man, T., Weiss, P.S., Monbouquette, H.G., 2021a. Implantable aptamer-field-effect transistor neuroprobes for in vivo neurotransmitter monitoring. *Sci. Adv.* 7 (48), eabj7422.
- Zhao, C., Liu, Q., Cheung, K.M., Liu, W., Yang, Q., Xu, X., Man, T., Weiss, P.S., Zhou, C., Andrews, A.M., 2021b. Narrower nanoribbon biosensors fabricated by chemical lift-off lithography show higher sensitivity. *ACS Nano* 15 (1), 904–915.
- Zhao, C., Man, T., Cao, Y., Weiss, P.S., Monbouquette, H.G., Andrews, A.M., 2022. Flexible and implantable polyimide aptamer-field-effect transistor biosensors. *ACS Sens.* 7 (12), 3644–3653.