Review Paper:

Potential Role of Neurotransmitters in the Development of Brain Cognitive Functions

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Abstract

Signal transmission is one of the important crucial phenomena responsible for the communication between two different synaptic neurons (pre and postsynaptic neurons) present in a brain region. This signal transmission is carried out by a specific group of chemical substances called neurotransmitters. These neurotransmitters are produced from the metabolic byproducts (precursor neurochemicals) transmitted from the gut to the central nervous system (CNS) through the blood-brain barrier (BBB). Transmitted precursor neurochemicals are further used by the presynaptic neurons for the biosynthesis of neurotransmitters for eliciting signal transmission with postsynaptic neurons. Synthesized neurotransmitters are released into the synaptic cleft for their binding with the postsynaptic neuronal receptors (PNR). The bound neurotransmitter along with the PNR complex further result in the activation of downstream signaling molecules (DSM) involved in various neuronal signaling pathways.

Activation of the DSM later results in the formation of cognitive memory against an unexposed stimulus. Formed memory is used by the organism for the differentiation of safe and unsafe stimuli in its living environment. In the present review, we reported the biosynthesis pathways involved in the production of neurotransmitters with the use of neuroactive chemicals and also stated the release and participation of neurotransmitters in the formation of cognitive memory with the help of recent findings. It also showed the effect of neurotransmitters in the development of cognitive dysfunctions. Thus the present review may act as a suitable platform for knowing the interrelationship of neurotransmitters and cognitive memory formation in a precise manner.

Keywords: Cognition, Memory formation, Neurotransmitter, Neurodegenerative disorders, Serotonin (5-HT).

Introduction

The three-pound organ, the brain, is also known as the control system of the human body. It controls and regulates every function in the body like breathing, maintaining body temperature, balance, motor functions and memory processing. Structurally, the brain is a complex organ consisting of more than 100 million neurons and is subdivided into the forebrain, midbrain and hindbrain with bundles of pre and postsynaptic neurons resulting in the formation of nerves and the nervous system[29,39]. These formed nervous systems run throughout the body and are categorized as central nervous system (CNS), peripheral nervous system (PNS) and autonomic nervous system (ANS).

The categorized nervous systems are responsible for information transmission from the body to the brain and vice-versa. Information transmission later on results in the formation of cognitive memory against an unexposed stimulus. Compared to other nervous systems, frontal brain regions are responsible for this memory formation by the synthesis of neurotransmitters in a regulated manner[10,11,19]. The current review discusses the production, release and role of neurotransmitters in cognitive memory formation.

Effect of Oral-gut communication in the synthesis of neurotransmitter precursors

The oral-gut-brain axis (OGBA) is one of the anatomical communications present in a host system. In this anatomical communication, the oral cavity (mouth) and gut (intestine) are in the line of the digestive tract with a constant relationship. In this connection, the vagus/trigeminal nerve connects the gut to the brain via the blood-brain barrier (BBB)[28,50]. The establishment of these connections in a host system results in the formation of a homeostasis mechanism between the brain regions in the central nervous system (CNS).

The formed brain homeostasis mechanism is a result of mutual interaction present between the oral cavity (OC) and the gut (G)[5,38]. The residential beneficial flora (RBF) of the OC and G plays a major in the synthesis of neurotransmitters through the supply of neurotransmitter precursor compounds (NPC) in the form of bioactive compounds, amino acid residue and metabolites. Initially, RBF produces metabolites like short-chain fatty acids, intestinal peptides and NPC through the process of metabolism and its relevant metabolic processes[27,57].

Further transported metabolites were used by the presynaptic neurons for the production of neurotransmitters (N). The produced N is later released into the synaptic cleft for its binding with the postsynaptic neuronal receptors. Further, the binding of N with the PSR resulted in the induction of calcium influx inside the postsynaptic neuron[15,17].

Increased calcium influx results in the activation of downstream signaling molecules like adenylyl cyclase (AC), cyclic adenosine monophosphate (cAMP), protein kinase A (PKA), extracellular regulated kinase – 1 (ERK -1). The regulated activation of AC, cAMP, PKA and ERK-1 results in the phosphorylation of cAMP response element binding protein-1 (CREB-1). Followed by phosphorylation, CREB-1 induces immediate early gene cascades and postsynaptic density proteins for the formation of long-term cognitive memory (LCM) in a normal condition [16,36,37]. In this OGBA, the production of N from the available NPC plays a major role in the formation of LCM by the use of various signaling molecules. Production of various N from NPC and its role in various cognitive processes were discussed elaborately to emphasize the role of neurotransmitters in the development of cognitive functions[30,31,52].

Neurotransmitter types and its role in the development of cognitive functions

Neurotransmitters are the chemical substances that are produced in the human body and are utilized by neurons to communicate with other neurons and their target tissue. The human nervous system contains more than 40 neurotransmitters, some important neurotransmitters among them are serotonin, dopamine, acetylcholine, gamma-aminobutyric acid (GABA), glutamate, norepinephrine and histamine[10,54].

Serotonin: Serotonin (5-hydroxytryptamine) is a type of monoamine neurotransmitter. It is derived from the amino acid tryptophan. Serotonin is involved in numerous human activities like mood, behavior, memory and many more. The high amount of serotonin is synthesized in the gut and secreted by the enterochromaffin (EC) cells present in the intestinal mucosa and in the central nervous system (CNS). It is synthesized in the raphe nuclei of the brain stem[1,25]. The biochemical synthesis of the serotonin involves the conversion of tryptophan (trp) into 5-hydroxytryptophan (5-HTP) with the help of tryptophan hydroxylase (TPH), then it is converted into serotonin by aromatic L-amino acid decarboxylase (AADC), the production of serotonin is dependent on the enzymatic cofactors tetrahydrobiopterin (BH4) and pyridoxine (vitamin B6)[24,60].

Further vesicular monoamine transporter packs the serotonin into vesicles. Later these packed vesicles are transported to the presynaptic nerve through fast anterograde axonal transportation and are released into the synaptic cleft for binding with the specific 5-HT receptors. Then the breakdown of serotonin takes place with the help of monoamine oxidase (MAO) which converts serotonin into 5-hydroxy indole acetaldehyde (5-HIAL) and 5-HIAL will be converted to 5-hydroxy indole acetic acid (5-HIAA) by aldehyde dehydrogenase (ALDH)[3,18]. These neurotransmitters have a wide range of roles in the human body. In CNS, it is widely known for its effects on mood, memory, stress, appetite, sleep, fear and pain perception. It also can activate ciliary body muscle that causes pupil dilation. Serotonin is involved in platelet aggregation as they are stored in platelet granules. It can contribute to vasodilation and can also increase gastric emptying, gut mobility and secretion in the intestine. Serotonin also regulates the endocrine system like pancreatic secretion, boosts insulin secretion, glucose uptake in muscle, lipid addition in the liver and lipogenesis. Excessive accumulation of serotonin and overstimulation on CNS and other organs is a condition called serotonin syndrome (SS) or serotonin toxicity (ST)[7,20].

Acetylcholine: Acetylcholine (ACh) is an ester of acetic acid (AcOH) and choline (Chol). It functions at the synapse between the muscle fiber and the motor neuron which is called neuromuscular junction. This neurotransmitter is synthesized in the presynaptic terminal and is synthesized from the acetyl coenzyme A (acetyl CoA) and choline with the help of the enzyme choline acetyltransferase (ChAT)[53]. Then this acetylcholine is packed into vesicles by the vesicular acetylcholine transporter.

In the central nervous system, it has roles in memory, motivation and attention. Acetylcholine originates from two major places in the brain which include the basal forebrain and the mesopontine tegmentum area. It is found that acetylcholine is known to affect a person's memory by preventing the learning of new information. The absence of acetylcholine in the hippocampus causes forgetfulness[43].

Norepinephrine: Norepinephrine or noradrenaline functions as both a neurotransmitter and a hormone. Its role as a neurotransmitter is important in the regulation of many cognitive functions and stress reactions in the brain. It is also involved in certain metabolic effects such as the induction of glycogenesis and gluconeogenesis[12].

It is also involved in hyperarousal or acute stress response as a hormone. The biosynthesis of norepinephrine involves the following steps: initially the tyrosine is converted into dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase, then dopamine is produced by decarboxylation of DOPA with the help of L-amino acid decarboxylase.

The produced dopamine is further transported into vesicle by vesicular monoamine transporter, here it will be converted to norepinephrine with the help of neurons that contain the enzyme, dopamine beta-hydroxylase. Then norepinephrine will be released to the synaptic cleft from the presynaptic terminal through exocytosis or further they can break down into epinephrine in the neurons that have phenyl ethanolamine-N-methyl transferase enzyme[6,22,44].

Dopamine: Dopamine contains 80 % of the total catecholamine present in the brain among mammals making it a catecholamine neurotransmitter and also known as a reward chemical of the brain. The biosynthesis of dopamine includes the conversion of tyrosine into dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase,

then dopamine is produced by decarboxylation of DOPA with the help of L-amino acid decarboxylase enzyme[41,58]. Later the dopamine is packed by vesicular monoamine transporter into synaptic vesicles. Dopamine is involved in cognition, frontal cortex functions like control of information flow in the frontal lobes. Any abnormalities in dopamine secretion in the frontal lobes can result in slow or declined neurocognitive functions like memory formation and it also plays a role in pleasure and motivation as it provides the feelings of excitement and enjoyment that motivate us to do certain activities[4,13,14].

Gamma-aminobutyric acid: Gamma-aminobutyric acid (GABA) is a derived product of glutamate (GLU) and is also an inhibitory neurotransmitter. GABA is present majorly in the spinal cord compared to the brain as an inhibitory neurotransmitter. The biosynthesis of GABA takes place in the presynaptic neuron's cytoplasm where glutamate is converted into gamma amino butyric acid (GABA) with the help of glutamate decarboxylase enzyme[26,40]. This enzyme requires vitamin B6 (pyridoxine) as a cofactor to complete the conversion of GABA. Then they are loaded into vesicles and are transported. These neurotransmitters bind to the GABA-A and GABA-B receptors in the post-synaptic neurons. GABA is involved in complex circuits in the CNS and connected with the inhibitory neurons which help to integrate excitatory proprioceptive signals that create smooth movements of the spinal cord[21,49,56].

Glutamate: Glutamate is an abundant amino acid present in the brain in the form of an excitatory neurotransmitter. In normal conditions, one type of the glutamate receptor will be expressed by most of the cells in the CNS. Some examples are N-methyl-D-aspartate (NMDA), kainite and a-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA). Glutamate is formed by the conversion of glutamine by the enzyme glutaminase[9,59]. This synthesis takes place in the presynaptic terminal and the vesicular glutamate transporter stores the packed vesicles. They are involved in many physiological functions as an amino acid and neurotransmitters; they also have certain effects on both injury and diseases. Neuronal excitability is controlled by glutamate synapse. They also play an important role in cognitive activities such as learning and memory[2,42].

Histamine: Histamine is a type of monoamine neurotransmitter and is known as a biogenic amine transmitter which is produced from histidine (H) with the help of the enzyme histidine decarboxylase (HDC). Similar to other neurotransmitters histamine is also packed by vesicular monoamine transporter into vesicles. Histamine contains the ability to control other neurotransmitters like serotonin and dopamine. They are also known as strong regulators of many hypothalamic functions such as neuroendocrine responses and are also involved in the regulation of oxytocin, adrenocorticotrophic hormone and prolactin. Histamine can also be a modulator of both water and food consumption. It contains other various roles such as thermoregulation, lipid metabolism, regulation of glucose, induction of reliving responses and many more[8,46,51]. As per recent studies, these neurotransmitters exhibit various roles in different body functions like muscle concentration, dilation of pupils, arousal and stress reaction. GABA as an inhibitory neurotransmitter inhibits nerve transmission to reduce neuronal excitability then glutamate regulates the spine density and sends signals all over the body by stimulating the neurons and histamines responsible for symptoms caused by allergies and maintain our sleep cycle[21,56].

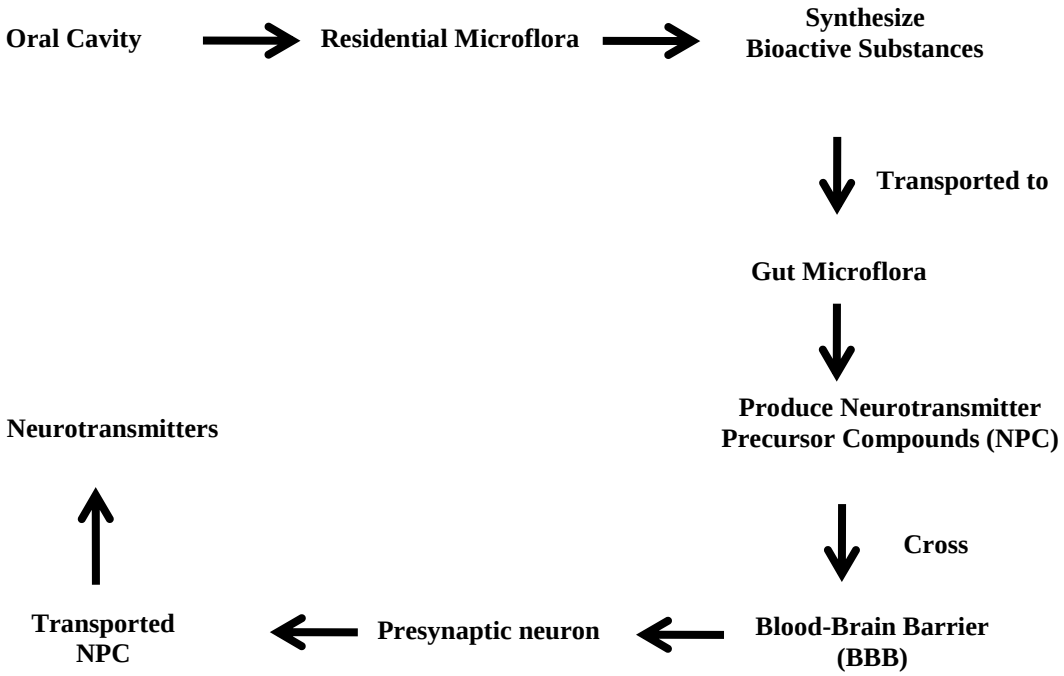


Figure 1: Flow diagram representing the production of neurotransmitters with the help of oral and gut microflora

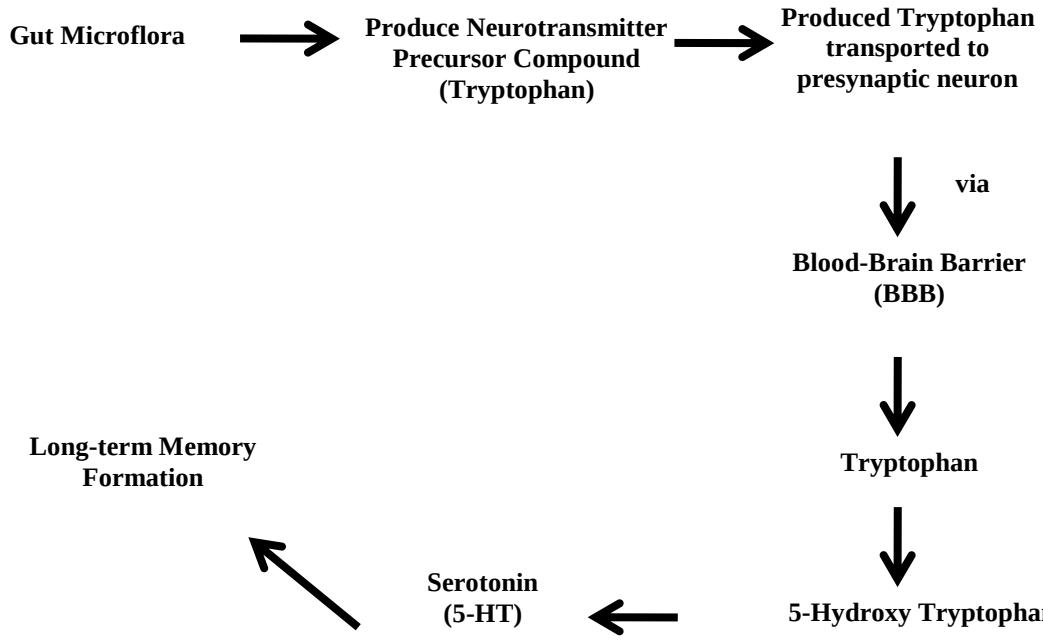
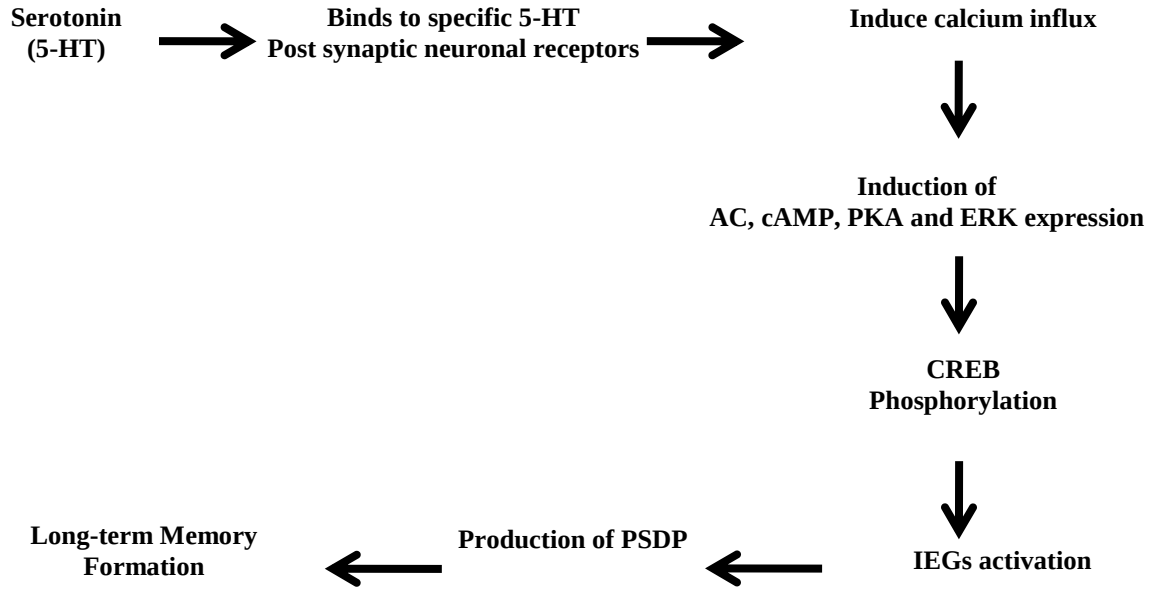


Figure 2: Representative flow diagram showing the biosynthesis of the neurotransmitter serotonin (5-HT) in the oral-gut-brain axis



AC – Adenylyl cyclase, cAMP – cyclic adenosine monophosphate, PKA – Protein kinase A, ERK – Extracellular regulated kinase, CREB – cAMP response element binding protein, IEGs – Immediate early genes, PSDP – Post synaptic density proteins

Figure 3: Role of serotonin (5-HT) in the development of long-term memory formation in the oral-gut-brain axis

Among these neurotransmitters, serotonin (5-HT) plays a vital role in memory formation by elevating the level of cAMP (cyclic adenosine 3`, 5`-monophosphate) in sensory neurons. Also, it assists in creating new neuronal pathways in the brain to strengthen the ability to learn quickly and cognitive function is boosted when the serotonin levels are higher[16,17,47].

Role of oral-gut-brain axis in the development of serotonin (5-HT) mediated cognitive memory formation

in normal condition: The neurotransmitter precursor compounds (NPC) present in the gut cross the blood-brain barrier (BBB) and reach the brain where they are used by the presynaptic neurons for the synthesis and release of neurotransmitters (N) into the synaptic cleft[10,15]. The released neurotransmitter (5-HT) binds to the specific postsynaptic 5-HT receptors which results in the activation of cyclic adenosine monophosphate (cAMP), protein kinase A (PKA) and enzyme-regulated kinase-1/2 (ERK-1/2) through the induction of calcium influx.

Table 1
Comparative analysis of healthy, dysbiosis and probiotic recovery state of oral and gut microflora showing the importance of the oral-gut-brain axis in the development of cognitive memory formation

	Normal condition	Oral-gut dysbiosis	Probiotic treatment
Oral flora[28,49]	Undisturbed	Disturbed	Recovered
Gut flora[28,49]	Undisturbed	Disturbed	Recovered
Neurotransmitter precursor compound (NPC) production[15,18]	High	Decreased	Regulated
Neuroinflammation[8,42]	Absent	Occurs	Reduced state
NPC transportation[20,30,33]	Regulated	Decreased	Recovered
Neurotransmitter production[1,3,10]	High	Low	Recovered to normal state
Expression of neuronal signaling molecules[35-37]	Increased expression	Reduced expression	Recovered to normal condition
Cognitive memory formation Level[31-33]	High	Low	Intermediate

These regulated levels of cAMP, PKA and ERK regulate the phosphorylation of CREB-1 (cAMP response element binding protein-1). The phosphorylated CREB-1 further induces the expression of immediate early genes (IEGs) and postsynaptic density (PSD) proteins. Induced IEGs and PSD result in the formation of long-term memory (LTM) with the help of transported NPC from the gut[35,37,54].

In disturbed condition: Poor oral hygiene reduces the beneficial microbes and increases the harmful microbes in the oral cavity as a result of pathogenic microbial colonization (PMC). The formed PMC results in the transportation of pathogens or its virulence factors to the gut which may cause an imbalance in the gut microflora. This imbalance in gut microflora may cause decline in the transmission of NPC from the gut to the brain as a result of oral and gut dysbiosis[30,32,33]. In the brain, the presence of reduced amount of NPC results in declined synthesis and release of 5-HT neurotransmitters. These reduced number of released neurotransmitters further bind to the specific postsynaptic 5-HT receptors which negatively regulate cAMP, PKA and ERK-1/2.

The negative regulation of cAMP, PKA and ERK-1/2 further affects the phosphorylation of CREB-1 with the downregulation of IEG and PSD proteins. Downregulation of IEG and PSD protein expression results in the formation of impaired LTM. Impaired LTM further initiates the development of cognitive impairment (CI) through induced oral and gut dysbiosis[32,33,45].

In recovered condition: To reverse the CI, probiotic strains were introduced into the oral cavity in the form of oral microbial infusions (OMI) which reduce the proliferation of harmful bacteria and restore the beneficial microbes in the oral cavity. Reduced proliferation of harmful bacteria may reduce the imbalance in the gut microflora and may regulate the expression of inflammatory mediators in the gut as a result of OMI[23,32]. The recovery of gut commensals may result in the proper transportation of NPC to the brain through the BBB. The transported NPC further syntheses and releases of neurotransmitters for the LTM formation through the neuronal signaling molecules like cAMP, PKA, CREB-1, IEGs and PSD proteins expression. The outcome of the recent studies showed that probiotic strains may reverse the induced cognitive impairment with the retrieval of commensals present in the oral cavity and gut[32,34].

Conclusion

In the present review, we have discussed the potential role of neurotransmitters in the development of cognitive memory formation through the OGBA. The unavoidable role of beneficial microorganisms presents in the OC and G in the production of neurotransmitters through the NPC. This review also discussed the types of neurotransmitters involved in cognitive functions like learning and memory, stress memory and fear memory formation. Other than neurotransmitter types, it also stated the unavoidable role of 5-HT in the formation of cognitive memory.

It elaborately emphasized the production of 5-HT from NPC (tryptophan) in normal, dysbiosis and recovered conditions concerning OGBA. In a normal condition, residential OC and G commensals play a major role in the supply of NPC in the required volume for the production of neurotransmitters in different brain regions. However, neurotransmitter production is reduced during the state of oral/gut dysbiosis through the decreased amount of NPC in the presynaptic neuron. During oral/gut dysbiosis, pathogenic colonization may reduce the synthesis of NPC through the aberration of oral and gut commensals in an increased manner.

Other than NPC reduction, it also induces inflammation reactions in the BBB and reduces the transportation of NPC from the gut to the brain. The reduced NPC synthesis can be recovered by the administration of probiotic microorganisms in a dose-dependent manner and maintaining proper commensals in the OC and G. Thus the presented review laid a path in understanding the role of neurotransmitter (5-HT) in the development of cognitive functions through the OGBA.

Acknowledgement
MM expresses sincere thanks to the Department of Science and Technology (DST), Government of India (GoI) for the establishment of the DST-FIST facility for Genomics and Proteomics in the Department of Biotechnology, Sri Ramakrishna College of Arts & Science (Autonomous), Coimbatore – 641 006, Tamil Nadu, India under the DST-FIST PG College Level – A Program (SR/FST/COLLEGE-/2022/1203).

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(Received 11th July 2024, accepted 13th September 2024)

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