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Review Article

Alzheimer's disease and traditional medicinal plants: A review

Debabrata Dash[1,*], **Raj Kumar Koiri**[1]

[1] *Dept. of Zoology, Dr. Harisingh Gour Vishwavidyalaya, Sagar, Madhya Pradesh, India*

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ABSTRACT

Alzheimer's disease (AD) is characterized by severe memory loss that affects one's ability to operate in social and professional contexts. More than 20 million individuals worldwide are affected by it, making it the most prevalent type of dementia. An elusive memory loss, corresponding functional deterioration, and behavioral abnormalities are hallmarks of AD. AD is the most common cause of disability in the elderly and patients may survive for more than ten years after receiving their diagnosis. From its lowest level at ages 65 to 70 to rates that may approach 6 percent for those over the age of 85, the incidence of AD ranges from 1 to 4 percent of the population per year. Over a hundred novel products are currently undergoing clinical trials thanks to ayurvedic medicinal plants, which have shown to be the most fruitful source of leads or medication development. Indeed, the use of several Ayurvedic medicinal plants and their ingredients for treating Alzheimer's disease has been detailed in a number of scientific research. Phytochemical analyses of the various plant parts have revealed the presence of numerous valuable compounds, including lignans, flavonoids, tannins, polyphenols, triterpenes, sterols, and alkaloids, that exhibit a wide range of pharmacological activities, including anti-inflammatory, anti-amyloidogenic, anticholinesterase, hypolipidemic, and antioxidant effects. However, the precise mechanism of their action is still unclear. This study compiles studies on several medicinal plants that have demonstrated potential for correcting the pathology of Alzheimer's disease. The report provides sufficient baseline data that could be used in drug discovery campaigns and development processes, thereby providing new functional leads for Alzheimer's disease. It does this by summarizing information regarding the phytochemistry, biological, and cellular activities, as well as the clinical applications, of these various plants.

1. Introduction

Alzheimer's disease (AD) is a condition marked by a progressive decline in cognitive ability and is brought on by plaque buildup in the hippocampal region of the brain. More than 5 million Americans have this condition, which is the most prevalent type of dementia in middle-aged and older persons; by 2030, it is projected that this number will rise to 7.7 million. Most cases of the disease develop after the age of 60, although some early-onset varieties are associated with a particular genetic flaw. Genetic factors undoubtedly play a part in 10% to 15% of cases, even though the etiology is unknown.[1] The efforts to develop a cure for AD have been incredibly unsuccessful thus far, and the treatments that are now used to treat the illness only effectively treat its symptoms. A loss of neurons in the hippocampus, cortex, and subcortical regions is the underlying etiology.[2] Short-term memory loss, difficulty learning new material, mood swings, trouble remembering words, forgetting names, and misplacing things are all early symptoms of AD. Patients with AD also frequently display aggression, irritation, and irritability. In severe situations, individuals lose all memory, sense of time and

* *Corresponding author*.
E-mail address: dashdebabrata97@gmail.com (D. Dash).

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place, and become entirely incontinent. Patients eventually need all-encompassing care as they become completely dependent on others. The patient must be placed in a nursing home with 24-hour nursing care because of their complete reliance on others. AD thus poses a significant challenge for patient management. According to estimates, the number of instances of AD would be drastically reduced within the next 50 years if treatment intervention could delay the disease's development or progression.[1]

2. Herbal Medicine

Simple herbal supplemental agents and therapeutic agents are included in the idea of HM in the conventional medical system. HMs can be made up of a single natural component, a fraction rich in a particular compound, a single medicinal plant, or a mixture of more than 10–20 different medicinal herbs. The World Health Organization (WHO) defined HM in 2005 as plant-derived products or preparations that have therapeutic or other advantages for human health and incorporate either raw or processed components from multiple plants.[3] According to the National Institutes of Health, HM is a type of natural product that is a part of complementary and alternative medicine (CAM) and is typically sold as a prescription pill or dietary supplement with the purpose of enhancing human health.[4] A conventional or orthodox drug, in contrast, is described as "a chemical substance utilized in the treatment, cure, prevention, or diagnosis of disease or used to otherwise increase physical or mental well-being". The general consensus is that HM contains many components made from a single plant extract or several different herbal medicines. In this essay, we examine how this term largely describes HM. CAM, a collection of non-conventional medical systems, includes the use of HM as one of its components in the treatment of disorders.[3] According to data from 2008, the HMs market is expected to exceed $60 billion annually.[5] According to estimates, 25% of all current medications come directly or indirectly from plants, including 60% of anti-tumor and antibacterial medications.[6] Nearly 65% of the world's nations have rules and regulations governing the use of HMs. The Dietary Supplement Health and Education Act, which was introduced as part of the Food and Drug Act (FDA) to regulate HMs, allowed for the registration of more over 20,000 herbal products as dietary supplements in the United States of America (USA).[7] Based on extensive or widespread traditional use, the FDA has designated about 250 herbs as "generally regarded as safe".[8] A registration system for HMs does not exist in the Netherlands, whereas 500 distinct types of HMs are licensed in the UK and about 3500 different types are registered in Germany. 657, 515, and 1242 HMs were registered in Asian nations using their respective registration processes: the Ayurvedic, Siddha, and Unani pharmacopoeias of India in India, the Korea pharmacopoeia and Korea herbal pharmacopoeia in Korea, and the Chinese pharmacopoeia in China. Instead of a registration system, Japan has an approval system; as of this writing, at least 1469 HMs have received approval.[3] HMs are handled in accordance with the combined laws of these nations as dietary supplements, over-the-counter medications, prescribed medications, self-medication only methods, or functional foods.

3. Pathophysiology of Alzheimer's disease

Although these characteristics are not always present, neuroimaging of a patient with AD or another dementia may indicate atrophy of the brain, including enlarged ventricles and sulci and narrower gyri.[9] The primary neuropathology factor behind AD symptoms is neuronal loss. Microscopically, senile plaques and neurofibrillary tangles are signs of Alzheimer's disease (NFTs). A protease cleavage result of the amyloid precursor protein, filamentous 3-amyloid, is seen in plaques, which are extracellular deposits.[10] The aberrant rearrangement of microtubule-associated proteins, such as tau, causes NFTs to develop intracellularly. NFTs and senile plaques are both present to some extent in the brains of healthy elderly people despite being diagnostic of AD when seen in high quantities. When AD is in its early stages or in normal brains, f-amyloid plaques are diffuse and often benign deposits; however, as the disease progresses, the plaques take on a compact b-pleated shape and are subsequently linked to dystrophic neuritis. These advanced plaques are considered to be a more neurotoxic variety.[11]

4. Cholinergic Hypothesis

Acetylcholine was the first neurotransmitter to be found to be defective in AD (ACh). It was found that the short-term memory impairment in AD was largely caused by a cholinergic deficiency since cholinergic function is necessary for short-term memory function. In the cortex and hippocampus, regions of the brain important in cognition and memory, markers for cholinergic neurons such as choline acetyltransferase and acetylcholinesterase, enzymes responsible for the synthesis and breakdown of ACh, respectively, are diminished.[12] Cholinergic neurons are primarily impacted in the nucleus basalis and the entorhinal cortex, where the earliest loss of neurons occurs. Up to 90% of the cholinergic neurons in the nucleus basalis of Mynert may go as the disease worsens.[13,14] Loss of cholinergic activity in these regions has been shown to be linked to reductions in learning ability and memory in animal studies. In the same way that dopaminergic impairments underlie Parkinson's disease and its clinical manifestations, it is believed that the resulting decrease in ACh-dependent neurotransmission causes the functional deficits in AD.[15,16] Drugs that increase ACh levels in the brain have been the

focus of clinical pharmacological trials in AD patients in an effort to make up for the loss of cholinergic function in the brain. ACh precursors, muscarinic agonists, nicotinic agonists, and cholinesterase inhibitors have all been used as these medications.[17,18] Cholinesterase inhibitors such as donepezil, rivastigmine, and galantamine are currently accessible and have been utilized in the best-developed and most successful methods to date.[19,20] Most of these drugs' studies have been conducted on AD patients, with the majority of them concentrating on those with mild to moderate disease. The most recent AD medication shifts away from ACh enhancement and concentrates on a different receptor complex. Memantine had been used for many years in Europe before it was authorized for the US market in October 2003. Patients with moderate to severe illness stages are targeted by the marketing of memantine.

5. Pharmacological and Herbal Treatment

ACh synapse degradation inhibitors are the mainstay of AD treatment, even though no medication has been demonstrated to entirely preserve neurons. The only medications recognized by the Food and Drug Administration as effective for treating AD are acetylcholinesterase/cholinesterase inhibitors and memantine. Although research has been done on other pharmaceuticals, their use is still debatable. Examples include selegiline, vitamin E, estrogen, and anti-inflammatory medications.[21,22] Ginkgo biloba is one of the many additional medications that have been tried in an effort to alter the course of AD or ameliorate its symptoms.[23–25] Tacrine, a cholinesterase inhibitor, is infrequently used because it could be hazardous to the liver and requires frequent laboratory monitoring. However, donepezil, rivastigmine, and galantamine frequently cause cholinergic side effects as nausea, anorexia, vomiting, and diarrhea. They also have low frequencies of significant adverse events. Only approximately 200 years ago, herbal medicines dominated the major pharmacopoeias, and many of the synthetic pharmaceuticals used today had their roots in the plant life. When basic and clinical pharmacology became the dominant fields of medicine, herbal medicine experienced a sharp downturn. However, there is ongoing interest in herbal treatment for many illnesses, including psychiatric and neurological conditions. There are several causes for this problem: Patients see that herbal medicine is consistent with their philosophical values and views, they are dissatisfied with conventional treatment, they want control over their healthcare decisions.[25] Numerous research and documentation suggest that herbal remedies have a special role in the treatment of AD. The study on several Ayurvedic medicinal herbs that have demonstrated potential in reversing AD pathology is compiled in the current review. The report provides sufficient baseline data that could be used in drug discovery campaigns and development processes, thereby supplying new functional leads for AD. It does this by summarizing information regarding the phytochemical, biological, and cellular activities as well as the clinical applications of these various plants. The different Ayurvedic nervine herbs that are suggested for AD and their effects on the brain are described here.

5.1. Ashwagandha (Withania somnifera)

As a nervine tonic, aphrodisiac, and "adaptogen," ashwagandha is widely used in Ayurveda to assist the body adapt to stress[26]. The root of ashwagandha, which belongs to the nightshade (Solanaceae) family, is the component that is most frequently used. It is classified as a rasayana (rejuvenative) and is thought to have antioxidant, free radical scavenging, and immune system-supporting properties.[27] Ashwagandha has a soothing impact in contrast to other adaptogens, which have a tendency to be stimulating, and may therefore be especially beneficial for persons with AD.[28] This herb may be used to induce relaxation since a complete alkaloid extract of ashwagandha root had a soothing impact on the central nervous system (CNS) in various mammalian species. In a recent double-blind, randomized, placebo-controlled trial on Ashwagandha's effects on stress, it was discovered that the herb's potential to improve focus and reduce symptoms of forgetfulness depended on dose, with 500 mg/day being more helpful.[29] There were no further negative consequences discovered. The steroidal lactones of the ergostane-type that are found in ashwagandha, such as the withanolides A to Y, dehydro withanolide R, withasomniferin A, withasomidienone, withasomniferols A to C, withaferin A, and withanone, are of significant interest to researchers. Other components include alkaloids (such as ashwagandhine, cuscohygrine, tropine, pseudotropine, isopelletierine, and anaferine), a range of amino acids (including tryptophan), high levels of iron, and phytosterols sitoindosides VII to X and beta-sitosterol.[30] Withanamides, a subgroup of these substances, have been demonstrated to scavenge free radicals produced during the onset and progression of AD. Withanamides also prevented the amyloid plaque-induced neuronal cell death.[31] According to molecular modelling studies, withanamides A and C specifically bind to the beta-active amyloid's motif (A 25–35) and stop the development of fibrils.[32] Ashwagandha has been shown to improve memory and learning in the CNS.[33] This herb's aqueous extracts have been shown to boost cholinergic activity, including acetylcholine content and cholineacetyl transferase activity in rats, which may help to explain some of the effects on cognition and memory.[34] Additionally, new studies have revealed fascinating details about this herb's capacity to promote neurite development.[35] In human neuroblastoma cells, treatment with the methanol extract of Ashwagandha

resulted in dose- and time-dependent neurite outgrowth. Ashwagandha was discovered to significantly raise the levels of the dendritic markers MAP2 and PSD-95 in cells, indicating that it promotes the growth of dendrites. In a follow-up study to the one mentioned above, the same research team gave amyloid peptide to cultured rat cortical neurons. This caused axonal and dendritic shrinkage as well as the loss of pre and postsynaptic stimuli. Following treatment with an Ashwagandha methanol extract, both axons and dendrites significantly recovered. Ashwagandha methanol extracts also restored pre- and post-synapses in the neurons and repaired the amyloid peptide-induced memory deficit in mice.[36] These Ashwagandha in vivo effects persisted long after the medicine had stopped being administered. Similar to this, preliminary studies from this dentate gyrus region only in J20 mice, mice that express the mutant form of human amyloid precursor protein (APP), bearing both the Swedish (K670N/M671L) and the Indiana (V717F) mutations, in comparison to J20 mice that only received normal chow (unpublished data). Additional clinical trials must be carried out to support Ashwagandha's therapeutic application, even if the data presented above are extremely encouraging for its use as an anti-AD drug. While the plant has been successfully utilized in Ayurvedic medicine for centuries, a comprehensive investigation of the acute or chronic toxicity of the herb or its numerous constituents is still absent, and more research is necessary to verify the herb's therapeutic value.[26]

5.2. Turmeric (Curcuma longa)

Turmeric comes from the plant Curcuma longa, often known as Haldi, and is used in curries and other hot cuisines from India, Asia, and the Middle East. Similar to many other herbal treatments, curcumin was first consumed as a meal before people realized it had powerful medical properties. Since ancient times, it has been widely utilized in Ayurveda (Indian system of medicine) as a painkilling and anti-inflammatory substance to treat pain and inflammation in the muscles and skin. It has also demonstrated anti-cancer qualities.[37] In Ayurvedic medicine, curcumin is revered as a "cleanser of the body," and now, science is uncovering an increasing number of diseases that can be treated by turmeric's active components.[38] Curcuma longa is the scientific name, and the Zingiberaceae family includes the gingers. Because it is sterile and does not generate seeds, turmeric is a plant. The plant bears dull yellow flowers and can reach heights of 3 to 5 feet. The plant's underground rhizomes or roots are used to make food and medicine. The rhizome is a thick, fleshy underground stem that is encircled by the bases of previous leaves. Turmeric is a recognizable bright yellow spice that is made from rhizomes that have been boiled, dried, and crushed.

5.2.1. Epidemiological studies of Alzheimer's disease and effect of curcumin

Numerous studies and research findings suggest that AD is less common and prevalent in India. In India, the prevalence of AD among persons aged 70 to 79 is 4.4 times lower than it is in the United States.[39] Researchers looked into the relationship between curry consumption and cognitive function in 1010 Asians between the ages of 60 and 93. According to the study, people who consume curry frequently (more than once a month) and sometimes (less than once a month) scored higher on the MMSE test of cognitive function than people who consume curry never or infrequently.[40]

5.2.2. Mechanism of action of curcumin on Alzheimer's disease

The method by which AD destroys nerve cells is thought to involve several characteristics, including metal toxicity, beta-amyloid plaque development, oxidative damage, and inflammation.

5.2.2.1. Curcumin on haemoxygenase pathway:. An effective inducer of hemoxygenase, a protein that offers effective cytoprotection against several types of oxidative stress, is the natural antioxidant curcumin. Curcumin stimulates hemoxygenase activity by encouraging the inactivation of the Nrf2-keap1 complex and enhanced binding to no-1ARE. An early rise in reduced glutathione was seen after astrocytes were incubated with curcumin at a concentration that encouraged hemoxygenase activity, and then a large rise in oxidized glutathione content.[41] Glutathione is a vital component for antioxidant enzymes that defend the mitochondria from endogenous oxygen radicals and is a significant antioxidant in the aqueous phase. Its level represents the body's ability to scavenge free radicals. Lipid peroxidation and oxidative damage result from GSH depletion, which harms tissues.

5.2.2.2. Beta-Amyloid plaques: . The presence of beta-amyloid plaques is the most obvious sign of AD. These plaques are essentially a collection of beta amyloid fibrils, which are tiny fibres. A proactive therapeutic approach for the treatment of AD would be the suppression of A-beta generation, prevention of A-beta fibril formation, and destabilization of pre-formed A-beta because the deposition of beta amyloid protein is a constant pathological hallmark of brains affected by AD. In compared to AD mice who did not get curcumin treatment, those that received low dosages of the herb saw a 40% reduction in beta-amyloid levels. Low doses of curcumin also resulted in a 43% reduction in the "plaque burden" that these beta-amyloid deposits had on AD mice's brains. Surprisingly, low dosages of curcumin administered over a longer period of time were actually more efficient than large doses at halting the neurodegenerative process associated

with AD.[42] Curcumin binds to amyloid beta and prevents its self-assembly at greater concentrations. Two aromatic end groups are among the key chemical characteristics of amyloid beta, and any changes to these groups have a significant impact on the protein's function. Curcumin crosses the blood brain barrier and attaches to plaques because of its lipophilic nature. Curcumin destabilizes the A-beta polymer and was a more effective inhibitor of A-beta 40 aggregation. Curcumin inhibits aggregation and disaggregates to generate fibrillar A-beta 40 in in vitro tests. A Japanese study found that curcumin destabilizes the fA-beta (1-40) and fA-beta (1-42) as well as their extension utilizing fluorescence spectroscopic examination with thioflavin T and electron microscopic analyses.[43] Isoxazoles and pyrazoles produced from curcumin bind to the amyloid beta peptide (Abeta) and prevent the metabolism of amyloid precursor protein (APP).[44] Multi-photon microscopy showed that curcumin penetrates the blood-brain barrier and shrinks the senile plaques after being administered to APPswe/PS1dE9 mice for seven days.[45] Another study found that curcumin increased the removal of amyloid-beta from the brains of AD patients through phagocytosis.[46] The chemical characteristics of curcumin that have been clinically examined and its varied effects on AD point to the possibility of doing additional research and developing more effective medications based on curcumin for treating AD.

5.3. Brahmi (Bacopa monnieri)

The bitter-tasting creeper plant brahmi, also known as bacopa, is typically used in Ayurvedic medicine as a nerve tonic, diuretic, and cardiotonic as well as a treatment for epilepsy, insomnia, asthma, and rheumatism.[47] Saponins and triterpenoid bacosapo nins, such as bacopasides III to V, bacosides A and B, and bacosaponins A, B, and C, are the main components of Bacopa monnieri (BM). The jujubogenin bisdesmosides bacopasaponins D, E, and F are additional saponin glycosides. Alkaloids, plant sterols, betulic acid, polyphenols, and sulfhydryl compounds are other components with antioxidant action.[48] The reduction of divalent metals, scavenging of reactive oxygen species, reduction of lipid peroxide production, and inhibition of lipoxygenase activity could all be effects of BM. Traditionally, BM was utilized to enhance cognition and memory. The neuropharmacological effects and nootropic properties of BM extracts have been thoroughly studied.[49] The fact that BM increases protein kinase activity in the hippocampus may play a role in its nootropic effects. In a rat model of AD, BM also prevented cholinergic degeneration and improved cognition. Additionally, a group of researchers discovered that a standardized extract of BM restored the cognitive abnormalities brought on by the administration of ibotenic acid and colchicines into the nucleus basalismagnocellularis by intracerebroventricular injection.[50] The frontal cortex and hippocampus's loss of acetylcholine, decline in choline acetyltransferase activity, and decline in muscarinic cholinergic receptor binding were all reversed by BM in the same trial. By inhibiting cellular acetylcholinesterase activity, BM extracts rescued neurons from beta-amyloid-induced cell death. Additionally, neurons exposed to BM extract had decreased levels of ROS, indicating that Brahmi reduced intracellular oxidative stress. In order to assess the short-term safety and tolerability of an increased phytochemical composition of BM in healthy adult volunteers. Clinical, hematological, biochemical, and electrocardiographic parameters were carefully examined, but none of the volunteers who took a single capsule containing the enriched herb orally for 30 days (300 mg for the first 15 days and 450 mg for the following 15 days) experienced any negative side effects.[51] The BM has now been offered in the Indian market for the treatment of memory and attention deficit disorders based on the aforementioned study and additional clinical studies conducted to establish the efficacy of BM in memory and attention disorders.[52] These clinical investigations with Bacopa serve as a guide for future research with additional herbs to determine their dose ranges that are beneficial, how long it takes to reach therapeutic levels, and how they affect the body over a longer period of time.

5.4. Gotu Kola (Centella asiatica)

Gotu kola is one of the key revitalizing herbs for nerve and brain cells in the Ayurvedic school of medicine and is thought to be able to increase intellect, lifespan, and memory.[53] There may be a role for gotu kola in the treatment and prevention of AD and beta-amyloid toxicity. Asiaticoside derivatives, such as asiatic acid and asiaticoside, have been shown to decrease hydrogen peroxide-induced cell death, decrease free radical concentrations, and inhibit beta-amyloid cell death in vitro.[54] In the brains of PSAPP (APP/ Sw x PS1M146L) mice, gotu kola extracts restored beta-amyloid pathology and altered the oxidative stress response.[55]

5.5. Jyotishmati (Celastrus paniculatus)

Jyotishmati is a prized medicinal plant that has long been utilized in Ayurveda to enhance memory, focus, and cognitive function because of its beneficial effects on the brain.[56] The aqueous extracts of CP seeds are antioxidant and cognitively stimulating. In part because of their antioxidant qualities and capacity to stimulate antioxidant enzymes, CP extracts rescued neuronal cells from H2O2-induced damage. By modifying glutamate receptor function, CP extracts also provided protection for neuronal cells from glutamate-induced damage. Additionally, the CP extracts shielded neuronal cells because of their capacity to stimulate the antioxidant enzyme catalase, reduce lipid peroxidation,

and scavenge free radicals. Additionally, CP seed aqueous extracts contain dose-dependent cholinergic action, which enhances memory function.[57]

5.6. Jatamansi (Nardostachys jatamansi)

Jatamansi is safe and has balancing effects, much like its relative valerian in Western culture. The plant has a long history of therapeutic usage and enjoys great respect in the Ayurvedic medical system. The plant's rhizomes and roots have been the subject of chemical research because they are useful as medicines.[58] Numerous sesquiterpenes and coumarins are present in them. One of the main ingredients of the root essential oil is the calming sesquiterpene valeranone, which is also present in valerian. Spirojatamol, nardostachysin, jatamols A and B, and calarenol are examples of further terpenoids. The main coumarin is jatamansi. Nardostachys jatamansi (NJ) extracts significantly reduced all of the symptoms of chronic fatigue syndrome (CFS) in rats, according to studies on the plant's function in the central nervous system. NJ extracts decreased CFS-induced elevations in lipid peroxidation, nitrite, and superoxide dismutase levels as well as low catalase levels. The information shows that NJ has strong antioxidant properties.[59] Similar to this, an alcoholic extract of this plant was given to young and old mice, and it dramatically enhanced learning and memory while also reversing the amnesia brought on by scopolamine and diazepam. Additionally, it corrected mice's naturally occurring aging-induced amnesia, indicating that the substances in this plant may be helpful in regaining memory in older people as well as in those suffering from age-related dementia.[60]

6. Conclusion

The creation of AD treatment methods has advanced greatly. Anti-inflammatory, anti-amyloid, anti-oxidant, and pro-cholinergic medications are a few of these tactics. For a therapeutic approach to be used successfully in clinical trials, it is important to have a better understanding of both the harmful and helpful effects of the medications. FDA-approved medications are currently available to treat AD symptoms and temporarily ease dementia. Though they typically have negative side effects, these medications do not treat the disease by changing its pathophysiology. The creation of alternative therapy modalities for AD remains very important. Recently, herbal medications have undergone extensive testing in human studies as well as in animal and cell models of AD. Herbal medications have fewer hazardous side effects, are easily absorbed via the BBB, and have a variety of synergistic effects, such as increased cognitive and cholinergic functioning. As a result, herbal medicines seem to be a potential complementary therapy for AD patients. However, more investigation into each herb's pathophysiology and phenotypic behavior in carefully planned clinical trials is required in order to evaluate their negative effects in AD patients.

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8. Conflicts of Interest

All contributing authors declare no conflicts of interest.

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Author biography

Debabrata Dash, Ph.D Scholar https://orcid.org/0000-0003-4625-4180

Raj Kumar Koiri, Assistant Professor https://orcid.org/0000-0002-1258-5160

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