

# AN EXTENSIVE REVIEW ON INTRICACIES OF AUTISM SPECTRUM DISORDER AND ASSOCIATED PHARMACOLOGICAL ACTIVITY OF CENTELLA ASIATICA

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## ABSTRACT

*A comprehensive study is undertaken on the functional development of brain in Autism Spectrum Disorder (ASD). Brain functionality trajectories are unique in autism spectrum disorder. Autism spectrum disorder (ASD) is a set of neuro developmental disorders characterized by a deficit in social behaviors and nonverbal interactions such as reduced eye contact, facial expression, and body gestures in the early childhood days till the age of three. It is not necessarily a single disorder, and it is broadly considered to be a multiple disorder resulting from genetic and non-genetic parameters and their interpretation. Hereditary study of ASD has acknowledged mutations that interfere with typical neurodevelopment in womb through childhood. These DNA complexities of genes have been involved in synaptogenesis and axon motility. Recent developments in neuroimaging studies have proved many vital perceptions in vivo into the pathological changes which occur in the patients' brain with ASD. Amygdala plays a major role in the limbic system and the affective loop of the cortico-striato-thalamo-cortical circuit, in cognition and ASD has been proved in various neuropathological and neuroimaging research findings. Besides the amygdala, the nucleus accumbens is also considered as the vital ingredient which is related with the social recognition response in ASD. Although educational and behavioral treatments have been the mainstay of the management of ASD, pharmacological and interventional treatments have also shown remarkable benefits in subjects with ASD. Also, there have been implications on few patients who experienced through one of the interventional treatments resulted improvement after deep brain stimulation. The key architecture of ASD development which could be the focus for intervention is still an untapped destination. Further work is needed to explore the horizons on the grey trajectories on ASD.*

**Key words:** Autistic Disorders, Review, Neurobiology, Amygdala

Autism spectrum disorder (ASD) is a developmental disorder categorized by deficits in social communication and repetitive and stereotyped interests and behaviors (Baio *et al.*, 2010). Autism is among the most enigmatic disorders of child development, with a dramatic increase in prevalence from 1 in 500 (0.20%) and incidence rate is approximately 1 in 90,666 in 2018 (according to Rehabilitation Council of India) (WHO., 2013). While the global burden of ASD is currently unknown, in the United States, the annual societal cost of the condition was recently predicted to be \$126 billion and \$34 billion in the UK (Lord *et al.*, 2020).

Currently, one of the most complicated issues among parents of wards with autism is disturbed sleep, with more than 40–80% of children afflicted with sleeping disorder, compared with 25–40% in typically developing children (TYP) (Reynolds *et al.*, 1978, Webster *et al.*, 1994).

The neuropathological basis of autism has not been experimented effectively and much of the work is focused on autism due to dysfunctions of mesolimbic (dopaminergic) brain areas (ventromedial prefrontal cortex, medial temporal lobe, striatum and limbic thalamus) because damage to these brain regions can cause frictions in autism (impaired social and emotional functioning, stereotyped behaviors,

mannerisms and obsessionist) (Málková L *et al*,2000).This hypothesis reported that (i) in animals, social deficits and stereotypical behavior are associated with damage to the medial temporal lobe in infancy(Bolton PF *et al*,1997) (ii) Autistic-type patterns of behavior with human are associated to abnormalities in the temporal lobe caused by other neurodevelopmental disorders (e.g. tuberous sclerosis) (Ozonoff S *et al*,1999)and (iii) individuals with autism are impaired on 'frontal' functional tasks (Zwaigenbaum L *et al*,2005) Non-limbic areas such as the parietal lobe have also been suggested as important in etiology because the inadequate attention span of the children with autism to salient social cues resemble distraction and neglect following parietal lobe damage (Cook Jr EH *et al*,1998) .Some children with autism are also impaired on neurological tests sensitive to parietal dysfunction(Courchesne E *et al*,1997). Other investigators have proposed that developmental abnormalities of the cerebellum (Chugani DC *et al*,1988) or dysfunction of cerebellar–cortical serotonergic pathways are patho-aetiological factors of autism (Schmahmann JD *et al*,1998) .Consistent with this, acquired cerebellar lesions have been associated with deficits in social and emotional behavior, functional dysfunction and possessiveness(Baron-Cohen S. *et al*,1988).

Recent studies on social deficits in autism have appeared (Kanner L. *et al*,1943)., so the relevant findings are only summarized here. Statistical study of Social Behavior is the earliest findings of the social impairment in autism (Kanner L. *et al*,1943)., These parameters result in the form of clinical impressions. This includes lack of "apparent affection", behavioural isolation, lack of attention towards people, use of nonverbal language poor communicative gestures, treating selected people as detached objects, poor eye contact, treating men as inanimate objects, lack of behavior inappropriate to cultural norms, attention to the nonsocial aspects of public, lack of awareness and poor empathy(Eisenberg L. *et al*,1943)., This escalation and economic problem help source individuals with ASD as one of the highest priority segments for clinical research and improvised treatment

The following are the list of few indications found among autism afflicted children

- They prefer to be alone.
- They never respond while addressed by name and behave as if they are deaf.
- Never show eye contact.
- Poor peer relationship with the same age group children.
- They do not point to ask for something.
- They never try to attract others by their activity.
- They never imitate adults 'action
- Never or rarely use gestures.
- Extreme fear syndrome
- They rejoice flapping, spinning, rotating objects
- Show dangerous distress in front of others

Behavioral studies have shown that typically developing (TD) children inherently value and pursue social stimuli such as a hug or smile from a parent (Wing L. *et al*,2004)., In contrast, individuals diagnosed with autism spectrum disorders (ASD) appear indifferent to faces and social interactions (Dawson G. *et al*,2004)

Clinical observations and previous studies suggest the hypothesis that early developmental dysfunction of brain pathways linking social stimuli and reward (Kishida KT, *et al*,1996) lead to autistic individuals' deficits in social and emotional reciprocity(Dawson G, *et al*,2010)

Dopaminergic predictions from the ventral tegmental area (VTA) to cortico limbic sections are significant in mediating the effects of repayment behavior (Capps L,1994)and neuroimaging studies have exposed that neural commotion in regions of the brain where dopaminergic neurons project, including the ventral medial prefrontal cortex, ventral striatum, posterior cingulate and precuneus, are modified by eye contact, a social reward signal( McClure SM *et al*,2003 )Dysfunctions in this pathway that may contribute to the lack of social motivation in ASD have also been previously explored using behavioral ( Kishida KT *et*

al,2003 )event-related potential (ERP), event-related potential (ERP) (Dawson G,*et al*,2005)and structural imaging studies(Dawson G,*et al*,2017).

Our brain is endowed with the ability to detect and respond to simple social signals such as eye contact, as well as to infer from more complex behaviors intrinsically social qualities of other people such as fairness or cooperation. Individuals suffering from high-functioning autism spectrum disorders (HFASD), a neurodevelopmental disorder, are impaired in understanding social cues and in responding to them. These patients generally have normal language or general intellectual abilities, yet in everyday life they avoid eye contact and do not spontaneously interact with people (Klin A *et al*,2005).On formal tests of social cognitive skill, they show specific impairments in understanding the intentions of others and lack of fast intuitive judgments about social contexts (Frith U.*et al*,2004) The pathogenesis of autism is unclear, although mutations in genes implicated in synaptogenesis have been identified (Dalton KM, *et al*,2005).and different neurochemical, neurophysiological, and neuropathological abnormalities have been demonstrated in these patients (Durand CM, *et al*,2007). An interesting current hypothesis has implicated oxytocin in the etiology of autism, and in the social disorders that are the hallmark of HF-ASD (Jamain *Set al*,2007).

There are many kinds of treatment available for autism such as Behavior and communication approaches, dietary approaches, Medication, Complementary and alternative medicines. Applied Behavior analysis, Physical therapy improves gross motor skills and helps to handle sensory integration issues (Durand CM *et al*,2007)Occupational therapy helps to treat sensory issues, sensory integration therapy, speech therapy improves communication skills.

Epidemiological survey of handicapped children in the London revealed that social impairment is not restricted to autism but is also found among other mentally handicapped people(Jamain *Set al*,,2007 ).They found that 21.2 of every 10,000 children aged under 15 years in the area exposed impairments of reciprocal interaction and, of these, 4.9 had a history of typical autism. Furthermore, they found that the social impairment could be distinguished into three types: social aloofness, passive interaction, and active-but-odd interaction. This latter description referred to social behavior that was undertaken mainly to indulge some repetitive, idiosyncratic preoccupation, showing no interest in the other person's needs.

Pharmacological treatment can help ameliorate some of the behavioral symptoms of ASD, including irritability, aggression and self-injuries behavior. Additionally, by reduce interfering disruptive behavior.

Social variationneedsdefinite cognitive and emotional capabilities. Specific Individuals with high-functioning autism or with Asperger syndrome cannot know or involve in communal situations in spite ofconservedrational abilities. It has been suggested recently that oxytocinhormone identified to encourage mother-infant ties, may be implicated in the social deficit of autism. The interactive effects of oxytocin with autism, in a replicated ball game where contestantscooperated with fictitious associates, found that after oxytocin inhalation, patients showed stronger connections with the most communally cooperative companion and reported better feelings of faith and preference. During free viewing of faces, oxytocin selectively enlarged patients' gazing periodon a social basiseducational region of the face, specifically the eyes. Thus, under oxytocin, patients respond more powerfully to others and displayed more appropriate social behavior and touch, signifying a beneficiallatent of oxytocin through its action on a centralmeasurement of autism (Waterhouse L *et al*,2007).

Risperidone is the initial FDA permittedmedicine for the treatment of indicativestate associate with ASD offspring and adolescence, including hostile behavior deliberate self-injury and annoyancepeevishness.

Aloneness and attachment were inspected in 22 high-operativeoffspring with autism and 19 characteristicallyevolving children associated with the autistic children for IQ, CA, gender, mom's education, and civilization. Children between the eons of 8 and 14 were requested to report on together their understanding and state of mind of solitude and the superiority of their relationship. Linked to typically emerging children, progenies with autism were both isolated and had fewerconsiderations of seclusion. All children with autism describedhavingas a minimum of one friend, the class of their

friendships was inferior in terms of comradeship, safety, and assistance. Scarcer associations were initiate between solitude and attachment for the autistic than for the non-autistic kids, portentousa lesser amount of empathetic of the next kin between lonesomeness and acquaintance. Implications of these results are discussed for hypothesizing the communal discrepancies in autism (Bauminger N, *et al*,2007).

Thus, the finding that abrasions to separate brain areas' outcome in clinical symptoms are also existing in people with autism mentions a neurobiological origin and involves dysfunction of the mesolimbic parts, parietal cortex and cerebellum. Though, the studies only deliver incomplete intuition into the genetic basis of autistic syndrome.

Research findings from scholars an overview since last two decades in pursuit of excellence in medical intervention & advancement in Pharma spectrum. A broad spectrum on pharmacological implications of *Centella asiatica* is furnished as below:

S.NO.	TOPIC	OBSERVATION	CONCLUSION	REFERENCES
1	The Medicinal Role of <i>Centella asiatica</i> and Its Applications in the Dahi	Thankuni extract is incorporated with dahi to improve the medicinal value. These properties have been ascribing to the active principles viz, Asiatic acid, Asiaticoside, Medecassocide,	These are Pentacyclic Triterpenes, found To Display Venous Insufficiency Various Vein and Wound Healing Properties.	(Kant, R., Srivastav, P. P., et.al,2019)
2	<u>Pharmacological Review on <i>Centella asiatica</i>: A Potential Herbal Cure-all</u>	The present review attempts to provide comprehensive information on pharmacology, mechanisms of action, various preclinical and clinical studies, safety precautions and current research prospects of the herb..	At the same time, studies to evaluate the likelihood of interactions with drugs and herbs on simultaneous use, which is imperative for optimal and safe utilization of the herb, are discussed	(Gohil KJ et.al.,2010)
3	<u><i>Centella asiatica</i> in cosmetology</u>	The mechanism of action involves promoting fibroblast proliferation and increasing the synthesis of collagen and intracellular fibronectin content and also improvement of the tensile strength of newly formed skin as well as inhibiting the inflammatory phase of hypertrophic scars and keloids.	Research results indicate that it can be used in the treatment of photoaging skin, cellulite and striae	(Bylka W et.al.,2013)

5	An in vitro study of the effect of <i>Centella asiatica</i> [Indian pennywort] on enteric pathogens.	Its potential as an antidiarrheal drug is worth studying.	The results of this study demonstrate the antimicrobial activity of <i>Centella asiatica</i> against the enteropathogens	(Mamtha B et.al,2004)
6	<i>Centella asiatica</i> (L.) Urban: From Traditional Medicine to Modern Medicine with Neuroprotective Potential", Evidence-Based Complementary and Alternative Medicine,	<i>C. asiatica</i> (gotu kola) has been reported to have a comprehensive neuroprotection by different modes of action such as enzyme inhibition, prevention of amyloid plaque formation in Alzheimer's disease, dopamine neurotoxicity in Parkinson's disease, and decreasing oxidative stress. Therefore.	<i>C. asiatica</i> could be suggested to be a desired phytopharmaceutical with neuroprotective effect emerged from traditional medicine	(Orhan IE, W et.al.,2012.)
7	Pharmacognostic, Phytochemical and Microbiological Studies of the Plants <i>Centella asiatica</i> (Linn.) Urban and <i>Withaniasomnifera</i> (Linn.) Dunal Treasured as Intelligence Boost.	ayurvedic preparations to encourage brainpower and remembrance as well as in various nerve disorders by virtue of their active constituents.	They are being widely used in various ayurvedic formulations to promote intellect and memory.	(Trivedi MN et al, 2011)
8	The present study was performed to evaluate the anti-ulcerogenic activity of ethanol extract of <i>Centella asiatica</i> against ethanol-induced gastric mucosal injury in rats.	The present finding suggests that <i>C. asiatica</i> leaf extract promotes ulcer protection activity of ethanol extract of <i>Centella asiatica</i> against ethanol-induced gastric mucosal injury in rats..	The present finding suggests that <i>C. asiatica</i> leaf extract promotes ulcer protection as ascertained grossly and histologically compared to the ulcer control group.	(Abdulla et al,2010)
9	<i>Centella asiatica</i> (L.) leaf extract treatment during the growth spurt period enhances hippocampal CA3 neuronal dendritic arborization in rats	The extract can be used for enhancing neuronal dendrites in stress	The growth spurt period enhances hippocampal CA3 neuronal dendritic arborization in rats and neurodegenerative and memory disorders	(Mohandas Rao KG et al, 2006)

10	Protective effects of <i>Centella asiatica</i> leaf extract on dimethyl nitrosamine-induced liver injury in rats.	The highest concentration of phytochemicals was found in the second accession that was asiaticoside (2.56 ug/ml), madecassoside (5.30 ug/ml) and asiatic acids (3421.60 ug/ml). Leaves contain a higher concentration of those phytochemicals relative to the petioles and the roots..	The findings suggested that in different parts of <i>Centella Asiatica</i> contain different amount of phytochemicals	(Choi MJ et al,2016)
11	Triterpene composition and bioactivities of <i>Centella asiatica</i> .	Triterpenes of <i>Centella</i> were measured using HPLC-PAD on an Excil ODS 5 mm (C18) column for the simultaneous determination of asiatic acid, madecassic acid, asiaticoside and madecassoside.	Leaves of <i>Centella asiatica</i> ( <i>Centella</i> ) were analysed for their triterpene composition and bioactivity such as collagen enhancement, antioxidant, anticellulite and UV protection capacity properties.	(Hashim P et al 2011)
12	LCMS/MS Metabolite Profiling and Analysis of Acute Toxicity Effect of the Ethanolic Extract of <i>Centella asiatica</i> on Zebrafish Model	This paper reports the qualitative and quantitative chemical analysis of the leaf ethanolic extract of <i>C. asiatica</i> using LCMS/MS.	The acute toxicity effect of the extract and selected marker chemical constituents were further analysed using a zebrafish model.	(Zakaria F, et al2019 )
13	Determination and quantification of asiaticoside in endophytic fungus from <i>Centella asiatica</i> (L.) Urban	This paper reported the production of asiaticoside by an endophytic fungus <i>C. gloeosporioides</i> for the first time..	The present findings definitely provide an impetus to the production of asiaticoside by utilizing the endophytic source	(Gupta S.et al, 2018 )

14	Centella asiatica phenolic extract-mediated bio-fabrication of silver nanoparticles: characterization, reduction of industrially relevant dyes in water and antimicrobial activities against foodborne pathogens.	In this article, we have reported an environmentally benign and cost-effective method for the synthesis of monodispersed silver nanoparticles (AgNPs), based on Centella asiatica phenolic extracts (CAPE).	The presence of phenolics was confirmed by ultra high-performance liquid chromatography coupled with electrospray ionization quadrupole time of flight mass spectrometry (UHPLC-ESI-qTOF-MS).	(EzeFN,et al2019)
15	Effect of temperature on the synthesis of Centella asiatica flavonoids extract-mediated gold nanoparticles: UV-visible spectra analyses.	In the present study, the initial synthesis of gold nanoparticles (GNPs) mediated by Centella asiatica crude flavonoids extract (CACrF) has been discussed. chloride, trihydrate (HAuCl <sub>4</sub> .3H <sub>2</sub> O) for the synthesis of GNPs.	The protocol involves a one-step, non-toxic and cost effective procedure based on green nanotechnology avoiding the use of any synthetic chemicals potentially harmful for environment and biomedical applications. The CACrF was reacted with gold	(Latif MS.etal,2018)
16	Centella asiatica: Plant with Immense Pharmacological Potential.	It can be used for rejuvenating as a nervine tonic. The present review attempts to provide comprehensive elevators phytochemistry, pharmacology, mechanisms of action, various preclinical and clinical studies and current research prospects of the herb.	In the present study, the initial synthesis of gold nanoparticles (GNPs) mediated by Centella asiatica crude flavonoids extract (CACrF) has been discussed. The protocol involves a one-step, non-toxic and cost effective procedure based on green nanotechnology avoiding the use of any synthetic chemicals	(AttreT.etal 2017)

			potentially harmful for environment and biomedical applications.	
17	A Literature Review of Pharmacological Agents to Improve Venous Leg Ulcer Healing. Wounds: a Compendium of Clinical Research and Practice.	Compression therapy is the gold standard treatment for venous leg ulcers (VLUs); however, with adjunctive pharmacological therapies and poor patient adherence using compressive dressings, clinicians are looking to find the advantage in treating VLUs.	This literature review focuses on the efficacy of pharmacological agents, quality of life using agents in addition to compression therapy, and cost effectiveness to indicate the best outcomes for pharmacological treatment of VLUs.	(Kitchens BP.etal,2020)
18	Pharmacokinetics of a standardized extract of Centella asiatica ECa 233 in rats	ECa 233, a standardized extract of Centella asiatica, has been found to exhibit various optimisticnervouswith uprightprotectionoutline.	positive neurological effects and to have a good safety profile.	(AnukunwithayaT,et al. 2017 )



19	Neuritogenic effect of standardized extract of <i>Centella asiatica</i> ECa233 on human neuroblastoma cells.	The present study clearly demonstrated neurite outgrowth promoting activity of ECa 233. ERK1/2 and Akt signaling pathways seemed to account for the neurotrophic effect observed. In conjunction with in vivo neuroprotective effect of ECa 233 previously reported, the results obtained support further development of ECa 233 for clinical use in neuronal injury or neurodegenerative diseases.	The results showed that all animals had a good tolerability for ECa 233, whereas madecassic and asiatic acids were found in negligible amounts after pharmacokinetic assessment. Madecassoside and asiaticoside demonstrated rather similar absorption and tissue distribution profiles. They were rapidly absorbed, reaching maximum levels within 5–15 min after oral administration, but they had poor oral bioavailability, less than 1%.	(Wanakhachornkrai.O,et al 2013)
20	Inverted U-shaped response of a standardized extract of <i>Centella asiatica</i> (ECa 233) on memory enhancement.	There was an inverted U-shaped response of ECa 233 on memory enhancement; 30 mg/kg maximally enhanced memory retention with an increase of synaptic plasticity and plasticity-related proteins in hippocampus.	Our data clearly support the beneficial effect on memory retention of a standardized extract of <i>Centella asiatica</i> within a specific therapeutic range.	(BoondamY,et al2019 )

21	Recent updates in neuroprotective and neuroregenerative potential of <i>Centella asiatica</i> .	. However, the capability of <i>C. asiatica</i> in enhancing neuroregeneration has not been studied much and is limited to the regeneration of crushed sciatic nerves and protection from neuronal injury in hypoxia conditions. More studies are still needed to identify the compounds and the mechanism of action of <i>C. asiatica</i> that are particularly involved in neuroprotection and neuroregeneration..	Furthermore, the extraction method, biochemical profile and dosage information of the <i>C. asiatica</i> extract need to be standardised to enhance the economic value of this traditional herb and to accelerate the entry of <i>C. asiatica</i> extracts into modern medicine. Recent studies have embarked on finding the molecular mechanism of neuroprotection by <i>C. asiatica</i> extract	(Lokanathan Y, et al 2016 )
22	A review on medicinal properties of <i>Centella asiatica</i> .	Many of its uses have been proven scientifically, and bioactive ingredients have been validated.	In this review, we have done a critical evaluation of available literature looking for the pharmacological importance of <i>C. asiatica</i> .	(Prakash V, et al 2017)
23	Effect of <i>Centella asiatica</i> Ethanol Extract in Spatial Working Memory on Adult Male Rats.	This study is aimed to investigate effect CeA ethanol extract on spatial working memory of normal adult male rats	<i>Centella asiatica</i> (CeA). CeA already known has some medicinal values for the brain such as to increase dendritic growth, to improve cognitive function and memory performance in rats after chronic stress..	(Suri AA, et al 2018 )

24	Evaluation of the Pre-Treatment Effect of Centella Asiatica Medicinal Plants on Long-Term potentiation (LTP) in Rat Model of Alzheimer's Disease	The present study was aimed to investigate the pre-treatment effect of Centella asiatica (CeA) extract on long-term potentiation (LTP) in a rat model of Alzheimer's disease (AD).the CeA extract had a preventive or protective role	.The present study showed that CeA had a protective role for neurons among rats with NBM lesion.	(Doulah A, et al 2020 ).
25	Comparative pharmacokinetics between madecassoside and asiaticoside presented in a standardised extract of Centella asiatica, ECa 233 and their respective pure compound given separately in rats.	study demonstrated that plasma levels of madecassoside, and to a lesser extent asiaticoside, were higher after administration of ECa 233 than the corresponding values for the pure compounds.	There was a bidirectional interconversion between asiaticoside and madecassoside consistent with the increased exposure of madecassoside and asiaticoside in ECa 233. 3.	(HengjumrutP,et al 2018 )
27	Phytochemical and pharmacological evaluation of organic and non-organic cultivated nutritional Centella asiatica collected after different time intervals of harvesting	Comparative phytochemical and pharmacological study of organic and nonorganic cultivated nutritional <i>C. asiatica</i> was done.	organically cultivated <i>C. asiatica</i> collected after first month proves to possess the best memory enhancing activity.	Bhattacharya RD,et al 2017
28	Functional constituents (micronutrients and phytochemicals) and antioxidant activity of Centella asiatica (L.) Urban leaves.	The present study investigated the genetic influence on phytochemistry of <i>C. asiatica</i> using 11 collections from Andaman Islands.	The study showed significant ( $p < 0.05$ ) variations in dietary micronutrients, potential antioxidants, and antioxidant activity.	(Singh S.et al 2014 )
29	Successful plant regeneration from callus cultures of Centella asiatica (Linn.) Urban.	The results from the phytochemical evaluations revealed that, the samples collected from first harvesting showed higher quantities of phytoconstituents.	The pharmacological evaluation included comparative nootropic activity of different samples of organic and nonorganic <i>C. asiatica</i> .	(Patra A, et al,1998 )

30	Stimulation of health-promoting triterpenoids accumulation in <i>Centella asiatica</i> (L.) Urban leaves triggered by postharvest application of methyl jasmonate and salicylic acid elicitors.	Our results suggest that MeJA and SA would be an exogenous elicitor	To enhance the triterpenoid contents after the postharvest process and increase anti-inflammatory activity in LPS-stimulated RAW 264.7 cells.	(Buraphaka H, et al 2020 )
31	Profiling of <i>Centella asiatica</i> (L.) Urban extract.	The highest concentration of phytochemicals was found in the second accession that was asiaticoside (2.56 ug/ml), madecassoside (5.30 ug/ml) and asiatic acids (3421.60 ug/ml). Leaves contain a higher concentration of those phytochemicals relative to the petioles and the roots	The findings suggested that in different parts of <i>Centella Asiatica</i> contain different amount of phytochemicals.	(ZainolNA,et al 2008)
31	Dopamine, a key factor of mitochondrial damage and neuronal toxicity on rotenone exposure and also parkinsonic motor dysfunction–impact of asiaticoside with a pro	Asiaticoside (AS), a triterpenoid saponin isolated from <i>Centella asiatica</i> was shown to exert a neuroprotective effect against hemiparkinsonism, purportedly due to phosphoinositides (PI)-assisted cytodynamics and synaptic function.	we evaluate AS in the modulation of dopamine (DA), mitochondrial integrity and neurite variations in vitro and motor dysfunctions in vivo.	(Margabandhu G, et al,2020 )
32	Pharmacological review on asiatic acid and its derivatives: a potential compound.	Asiatic acid (AA), a naturally occurring pentacyclic triterpenoid, is found mainly in the traditional medicinal herb <i>Centella asiatica</i> .the pharmacological activities of AA were compared with two natural compounds: curcumin and	. This review summarizes the research on AA and its derivatives and helps to provide future directions in the area of drug development..	(LvJ,et al Sharma A, 2018 )

		resveratrol		
33	Centella asiatica in dermatology: an overview.	The mechanism of action involves promoting fibroblast proliferation and increasing the synthesis of collagen and intracellular fibronectin content and also improvement of the tensile strength of newly formed skin as well as inhibiting the inflammatory phase of hypertrophic scars and keloids.	Research results indicate that it can be used in the treatment of photoaging skin, cellulite and striae	( Bylka Wet al, 2014 )
34	Current updates on Centella asiatica: phytochemistry, pharmacology and traditional uses.	The present review summarized widespread information on phytochemistry, isolated and characterized bioactive compounds, pharmacological properties, in vitro propagation and traditional uses of the important medicinal plant <i>C. asiatica</i> .	The asiatica is also rich in flavonoids and terpenoids compounds among them asiatic acid, asiaticoside, madecassoside is well characterized for its pharmacological value.	(Roy DC et al., 2013)
35	Caffeoylquinic acids in Centella asiatica protect against amyloid- $\beta$ toxicity.	The important markers for future studies on CAW standardization, bioavailability, and dosing.	It is demonstrated that treatment with the water extract of Centella asiatica (CAW) improves learning and memory deficits in Tg2576 mice, an animal model of A $\beta$ accumulation. These data suggest that	(Gray NE,et al 2014)

			CQAs are active neuroprotective components	
36	In vitro and In vivo wound healing studies of methanolic fraction of <i>Centella asiatica</i> extract.	The recent findings suggest that methanol fraction of <i>C. asiatica</i> demonstrated remarkable polyvalent activity, and thus has potential as an effective wound healer	. In conclusion, the claim of the presence of wound healing properties in <i>C. asiatica</i> had been well supported based on the results obtained in this study.	(Azis HA, et al 2017 )
37	<i>Centella asiatica</i> extract protects against amyloid $\beta_{1-40}$ -induced neurotoxicity in neuronal cells by activating the antioxidative defence system.	CAE-mediated protection against aggregated $A\beta_{1-40}$ -induced neurotoxicity is attributable to modulation of the antioxidative defense system in cells by CAE.	This emphasizes the potential therapeutic and preventive value of CAE in the treatment of AD.	(Chen CL,et al, 2016 )

### Conclusion

The main goal of my Autism Research is to learn more about the cause of Autism and to promote drugs which can improve the quality of life of people living with this ailment in different degrees. Based on my extensive research findings and most of the above proven solutions over two decades of study by my predecessors the extract of *Centella asiatica* showed a significant role in neuroprotective functionalities. The prevalence of Autism is increased significantly due to lack of suitable diagnostic tools in prenatal condition, this increase may be largely attributed to broader diagnostic criteria and one of the key objective is to enable a new level of research that was not possible previously on animal studies through prenatal intervention of the extract of *Centella asiatica* in animal model. Receiving an accurate Autism spectrum diagnosis at younger age is associated with more positive functional outcomes in later life as a result of ASD diagnosis and receipt of the above targeted treatment. Since there is no ample evidence in support of Autism care and permanent cure pragmatically.

The above situation inspired me to contribute something constructively to address the society afflicted by this disorder which is not adequately analyzed hitherto considering the density of this disorder and mental agony encountered by the parents' siblings of the Autism affected kids is inexplicable. Here again according to my understanding Autism is more prone among boys as compared with girls (4:1) ratio remarkably alarming. Hence requiring utmost care to be attached to identify remedial medicines are explored in a quickest pace to reduce further autism penetration across the globe.

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