

## Hampering Essential Tremor Neurodegeneration in Essential Tremor: Present and Future Directions

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**Abstract:** Essential tremor (ET) is one of the most prevalent neurological disorders worldwide. ET presents mainly with kinetic and action tremor in upper limbs. Tremor may also affect the head and some patients develop an ataxic gait, as well as cognitive/affective symptoms. ET significantly impacts the quality of life. There is accumulating evidence that ET is a slowly progressive neurodegenerative disease, driven by both genetic and environmental (possibly dietary) factors. Both the olivocerebellar pathways and the cerebellar cortex are critically involved, with particular impairments in the morphology of the Purkinje neurons (Purkinjopathy) as well as the surrounding micro-circuitry. Dysfunctional cerebello-thalamo-cortical loops probably result in bursts of tremor. So far, only few symptomatic medications are available, including beta-blockers, primidone and drugs aiming to modulate GABAergic transmission such as topiramate or gabapentine. Surgery (deep brain stimulation, thalamotomy) is proposed to refractory cases but carries the risk of infection, bleeding in the brain and several technical issues related to the mispositioning of electrodes. MRI-guided focused ultrasound is a promising technique, but long-term follow-up is missing. Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are encouraging non-invasive techniques but no consensus on optimal protocols has been reached so far. It is remarkable to observe that none of the available therapies targets the neurodegenerative process affecting in particular the cerebellum, the masterpiece of progression of the disease. This chapter focuses on the pathogenesis of ET and discusses possible novel avenues for therapy and prevention. In particular, the impact of environmental toxins such as beta-carboline alkaloids ( $\beta$ CAs), possibly generated from Maillard-type reaction products, is discussed. Animal models of ET, toxicokinetics and neurotoxic effects of  $\beta$ CAs are presented, with an emphasis on the neuroprotective pathways that are candidates to block the neurodegenerative process. Moreover, we consider a group of enzymes that could be neuroprotective, especially GAD65 and GAD67, involved in GABA synthesis/neurotransmission, and MAO<sub>A</sub>/MAO<sub>B</sub>. Finally, we emphasize the potential interest of dietary phytochemicals (such as phenolic acids, catechins, flavonoids, anthocyanins, stilbenoids, curcuminoids)

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and herbal therapies (based *i.e.* on *Bacopa monnieri*, *Ginkgo biloba*) as neuroprotective approaches to hamper the neurodegenerative process in ET.

**Keywords:**  $\beta$ -Carboline Alkaloids, Chemoprevention, CNS Disorder, Deep Brain Stimulation of the Thalamus, Essential Tremor (ET), ET Pharmacotherapy, ET Animal Model, (GABA)ergic Dysfunction, Gamma Knife Surgery (GK), Harmane, Harmaline, Maillard Reaction, Neuroprotection, Neurodegenerative, Neurotoxicity, Purkinje Neurons, Repetitive Transcranial Magnetic Stimulation (rTMS), Thalamotomy.

### **ESSENTIAL TREMOR: DEFINITION AND EPIDEMIOLOGY**

Essential tremor (ET) is characterized by a slowly progressive postural and/or kinetic involuntary tremor, a bilateral action tremor affecting predominantly the arms, the head and/or the voice [1]. ET is primarily a kinetic tremor; the main clinical features of ET consist in kinetic tremor of the arms (tremor occurring during guided voluntary movements) with frequencies of 4 to 12 Hz, followed by postural and/or kinetic tremor of cranial structures (*i.e.* neck, jaw, voice) [2]. Patients usually first become aware of the tremor when they are holding newspaper or utensils or when reaching for objects. When ET affects the neck muscles, patients exhibit either yes-yes or no-no oscillations of the head. Furthermore, ET can affect the vocal cords, causing a tremulous voice while singing or talking [3]. As time evolves, ET tends to impair balance and gait, and may even cause falls.

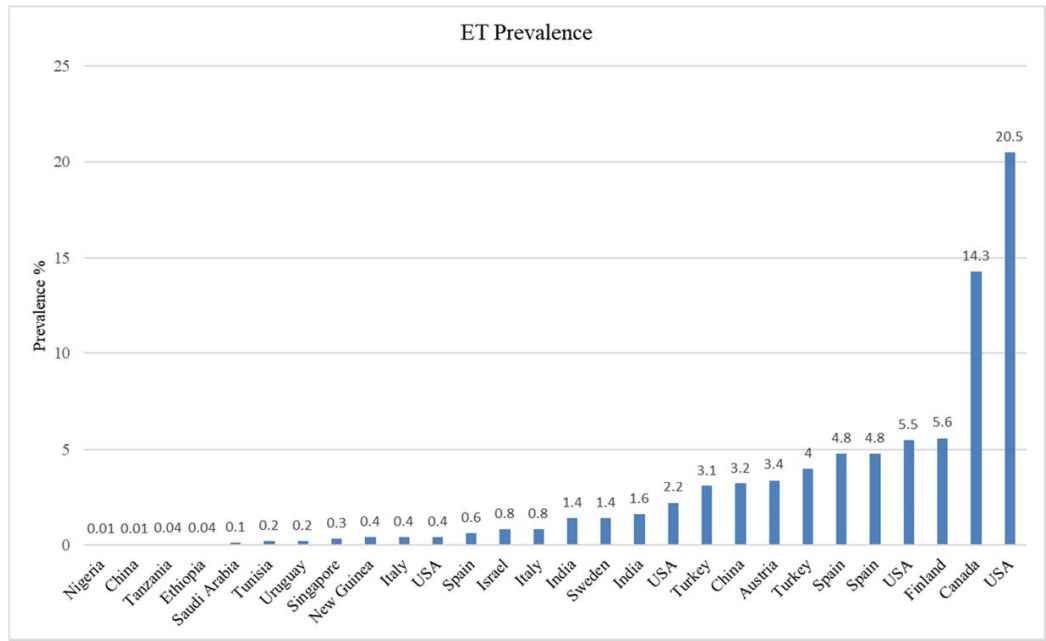
Apart from the first group of motor features, recent research points out a variety of cognitive and psychiatric signs. One of the most common non-motor symptoms in ET is the presence of mild cognitive deficits [4], notably for verbal fluency, naming, mental set-shifting, verbal memory, and working memory; deficits in olfaction and hearing loss have also been observed in ET but the published studies remain inconclusive [5]. Significant relationships are reported between ET and depression [5], poor nocturnal sleep quality and sleep disturbances [6]. Non-motor symptoms could be a part of the disease in the early stages; indeed depression and anxiety are more common in young patients with ET [6]. In fact, depressive symptoms appear to be stronger predictors of tremor-lowered quality of life than the motor aspects of tremor itself [7].

Obviously, and even if some patients will never come to medical attention, both motor and non-motor ET symptoms result in significant psychosocial and physical disabilities, interfering with activities of daily living (ADL) such as eating, drinking, writing [3]. The classical view of ET as a monosymptomatic condition is now replaced by the concept of a heterogeneous disorder with

multiple motor and non-motor features of varying degrees.

**Incidence and Prevalence**

ET is among the most prevalent disabling and poorly understood neurological movement disorders, especially affecting elderly people, but also appearing in young adults and even during childhood [8]. The disease has been reported not only by neurologists, but also by internists, geriatricians, and general practitioners [9]. The adjusted incidence is about 619 per 100.000 person-years among persons aged 65 and older [10]. However, the prevalence estimates have varied enormously amongst studies and it is therefore difficult to establish the prevalence at a world level. A meta-analysis by Louis and Ferreira identified 28 studies over 19 countries, with prevalence ranging from 0.01% (Nigeria, China; all ages) to 20.5% (USA; over 65 years) (Fig. 1). By pooling prevalence in all age classes, the



**Fig. (1).** Studies are ordered from lowest to highest prevalence (expressed in %). There are differences between studies regarding the screening process and epidemiological methods, in addition of variability in terms of age of examined subjects (notably, Canadian and US studies gather mainly patients in the elderly) [Adapted from [11]].

worldwide prevalence was then estimated at 0.9%. The prevalence markedly increased with age (4.6% for age ≥ 65 years), and especially with advanced age.

Although data are quite incomplete in numerous cases, the prevalence of ET may show regional and possibly ethnic differences. A majority of studies do not show a gender difference in ET prevalence (ratio men to women of 1.08:1.00); 6 studies indicate a gender imbalance (5 studies; ratio men: women 1.65:1.00) whereas one study indicates higher prevalence in women (ratio men: women 0.39:1.00) [11].

The very high incidence and prevalence raise the question of a predisposition to the disease [8]. Age is clearly a risk factor for ET. Most studies indicate a marked age-associated rise so that prevalence may be higher than 20% in the oldest patients [11].

### **PATHOGENESIS**

ET is a complex disorder, poorly understood both in terms of etiology or pathophysiology. Epidemiological data suggest that a combination of genetic abnormalities with putative non-genetic (*e.g.*, environmental) factors lead to a slowly progressive neurodegeneration that causes shaking and other disturbances of neurologic function.

Many hypotheses relate to the etiology of ET, with two dominant central models – a conventional physiological model, also called “*olivary model*”, and the more recent “*degenerative cerebellar model*”, underpinned by molecular mechanism, cell biology and anatomo-pathology.

In the first model, ET would be in essence a primary electrical/electro physiological disorder, resulting from the overactivity of pacemaking neurons located in the inferior olivary nucleus. These neurons, which are coupled by gap junctions, fire in a rhythmic manner and target the Purkinje neurons in both the cerebellar cortex and cerebellar nuclei. The over-activity of the inferior olive would lead to a rhythmical burst firing in the cerebellar cortex and cerebellar nuclei (the sole output of the cerebellar circuitry), therefore producing tremor through an abnormal olivo–cerebellar activity and *via* the cerebello-thalamo–cortical output channels [12].

This model, which puts forward the inferior olive as the pacemaker of ET, was recently surpassed by a degenerative cerebellar cortical model based on intensive tissue-based studies that identified structural changes within the cerebellar cortex circuitry itself. Indeed, a loss of Purkinje cells was demonstrated by post-mortem investigations in ET cases using cells count, as well as linear density measurements [13]. The population of Purkinje cells would in fact represent the site of initial molecular/cellular events (hence the terminology of “*purkinjopathy*”) [14], generating a secondary remodeling/rewiring within the cerebellar cortex, with subsequent changes in adjacent neuronal populations

(mainly the interneurons surrounding the Purkinje neurons). The formation of this aberrant cerebellar circuitry is probably central to the pathogenesis of ET, with notably thickened axons and remodeled basket cells [15, 16].

ET, as a progressive, age-related, disease, appears indeed truly *neurodegenerative* in nature [17]. This theory is further supported by evidence of brain iron accumulation [18]. Such iron deposits have been observed in other neurodegenerative disorders, such as Alzheimer's, Parkinson's and Huntington's diseases, that are also progressive disorders associated with ageing. In all these devastating disorders, cell loss occurs in combination with other cerebral changes or deposits (such as Lewy bodies for instance) [19]. It is noteworthy that the phenotype of these diseases includes a constellation of motor/non-motor dysfunctions [20].

However, the neurodegenerative hypothesis does not explain the early onset cases and the clinically very slow and heterogeneous progression of ET in other cases. Some patients show combinations of tremor and minor cerebellar symptoms with no evidence of other brain structures involvement. Furthermore, although there are clinical and electrophysiological arguments of cerebellar manifestations in ET patients, the reversibility of these symptoms and signs by ethanol intake (or thalamic deep brain stimulation: DBS; this is a matter of debate) challenges the neurodegenerative hypothesis [21, 22]. Some may claim that DBS is very active in Parkinson's disease whose pathogenesis is clearly neurodegenerative. Moreover, it can be argued that the Purkinje cell loss could be the result of long-standing tremor and not its cause (given that the cerebellum receives numerous afferences *via* the spinocerebellar pathways and the pontocerebellar tracts), although one would expect a progressive cerebellar degeneration in all steady tremor conditions if this were true [5].

An alternative hypothesis to ET genesis is based on inherent neural instability that leads to the generation of rhythmic bursts in central oscillating pacemakers such as thalamic nuclei (neurons of the inferior olivary complex also fall in this category). Through their tight interconnections within motor system networks, these oscillators become entrained, coupling their firing patterns to result in visible and pathologic tremors. This view can account at least partially for the heterogeneity of ET manifestations and therapeutic responses. Although structural alterations are not a pre-requisite for a neural instability, a pre-existing structural damage in the brain is a likely ground [5, 23]. Reports highlight that key structures involved in tremor genesis such as thalamic nuclei and the inferior olivary complex are normal. Furthermore, the fact that degeneration of inferior olive does not lessen tremor reinforces the concept that the inferior olivary

nucleus does not play a critical role in the generation of tremor in these patients [24].

Neuroimaging studies have provided arguments for a disorder of the CNS. Reported outcomes from fMRI (functional Magnetic Resonance Imaging) and cortico-muscular MEG (Magneto Encephalography) analyses indicate that ET is mainly a disease of central origin, involving in particular 3 key-nodes within the numerous brain networks: the cerebellum, the thalamus and the primary motor cortex [25, 26]. PET (Positron Emission Tomography) studies suggest a gamma-aminobutyric acid (GABA)ergic dysfunction in tremor generation. A correlation has been identified between flumazenil uptake (flumazenil is a selective benzodiazepine receptor antagonist) and tremor rating scales, pointing towards abnormalities in GABA receptor binding. This defect would lead to a lack of inhibition within the cerebellar microcircuits, especially at level of the cortico-nuclear synapses between Purkinje and cerebellar nuclei neurons; the resulting glutamatergic overactivity (disinhibition of cerebellar nuclei) would generate tremor along the cerebello-thalamo-cortical pathways [27, 28]. This mechanism is supported by the observation that ET is highly responsive to ethanol, benzodiazepines and barbiturates, which all facilitate inhibitory neurotransmission by binding to the GABA<sub>A</sub> receptor in the brain [29]. A pharmacological correction of GABA dysfunction could thus have a potential therapeutic effect in ET.

### **Etiology**

ET might be triggered by a combination of both intrinsic and extrinsic mechanisms. Regarding the latter, environmental risk factors probably contribute to the etiology in a considerable proportion of cases. Yet there has been relatively little discussion in the tremor literature about a clear identification of these factors. Exposure to beta-carbolines, mercury, lead, organochlorine pesticides have all been incriminated [30]. Harmane, a heterocyclic amine (HCA)  $\beta$ -carboline alkaloid ( $\beta$ CA), is a potent tremor-producing neurotoxin. It is often found in the human diet and therefore a lifelong exposure is plausible. Blood concentrations are elevated in patients with ET as compared with controls and increased blood harmane concentration could be associated with cerebellar neuronal damage [31]. Louis *et al.* have demonstrated a strong inverse correlation between cerebellar N-acetyl aspartate to creatine ratio (NAA/Cr; a marker of neuronal damage) and blood harmane concentrations in 12 ET cases [31]. The correlation was absent in other brain regions such as thalamus and basal ganglia, or with other neurotoxins such as lead or manganese. In addition, animal studies have demonstrated that harmane and other  $\beta$ CAs produce cerebral damage. However, further confirmations on human post-mortem tissues, including accurate measurements of  $\beta$ CAs levels, are needed [30]. In order to avoid

artifactual  $\beta$ CAs formation, tissues from autopsies should be preserved without formol/formaline solutions.

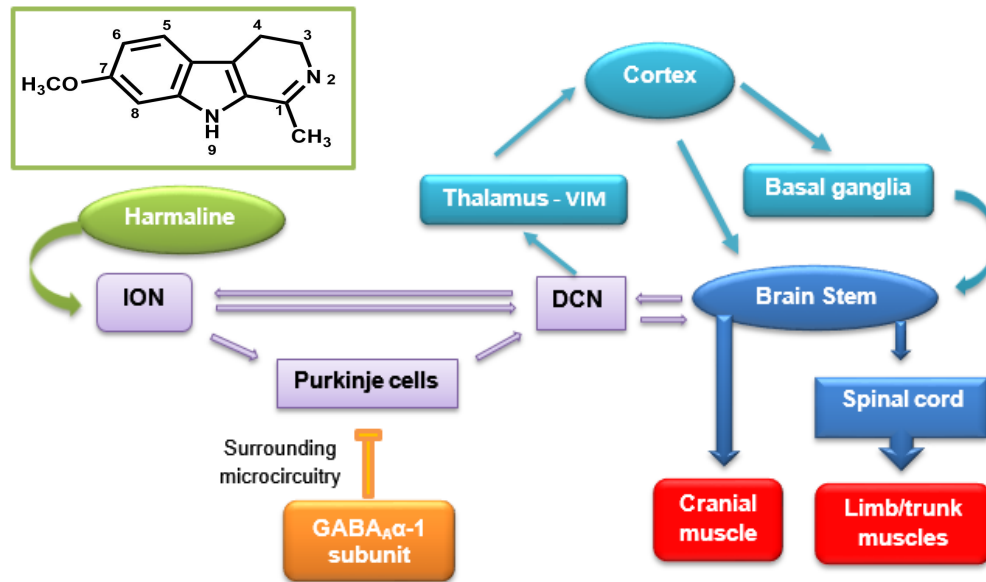
## **EXPERIMENTAL ANIMAL MODELS OF ET**

Animal models of tremor have been developed in experimental neurology, because they remain a cornerstone, not only for understanding the pathophysiology of human tremor disorders, but also for the development of novel therapeutic agents. At least two approaches have been used to trigger, in animals, tremor reminiscent of ET: (1) administration of tremorgenic drugs such as harmaline, (2) use of various inbred strains.

Harmaline-induced tremor in rodent has been proposed as a possible model of essential tremor [32]. There are similarities between the two conditions, in particular the attenuation induced by ethanol [33]. Harmaline induces an action tremor with both kinetic and postural components. Anatomically, neurons of the inferior olivary nucleus (ION) have excitatory projections to the Purkinje cells of the cerebellar cortex (climbing fibers). As mentioned earlier, the ION neurons are electrically coupled and generate synchronous oscillations of membrane potentials. Harmaline acts directly on ION neurons, modulating their rhythm-generating ionic currents and facilitating rhythmic discharges. In rodents, it is presumed that harmaline-induced bursting is transmitted from the cerebellum to motor neurons in the spinal cord *via* the brainstem, thus resulting in generalized tremor (Fig. 2). However, three points have questioned the relevance of this model for the pathophysiology of ET, (*i*) the primary target of harmaline: the role of the ION neurons remains controversial in ET and harmaline interferes also directly with several brain neurotransmitters; (*ii*) the transmission pathways: in ET, the cerebello-thalamo-cortical pathways are considered as the main route of electrical bursts spreading from the cerebellar circuitry towards the motor cortex and subsequently from the motor cortex to the motor neurons of the spinal cord; and (*iii*) species-specific differences have been observed in the response of the olivocerebellar system to harmaline and in the vulnerability of the Purkinje cell layer [34] (Fig. 2).

A survey of animal models with chronic partial purkinje cells loss has been reviewed [35] since clinical studies suggest relation between purkinje cells loss and ET [13]. There is a limitation in the reviewed studies as tremor was not the primary interest; in addition, there were no constant results. Some models with chronic severe loss of purkinje cells show no tremor *i.e.* Purkinje cell degeneration mouse where the lost purkinje cells axon terminals on DCN neurons are replaced by astrocytic glial leaflets [36]. While other models with acute severe loss or chronic partial loss of purkinje cells may display tremor, *i.e.* Weaver

mouse, scrambler mice, sticky mouse, toppler mice, WDR81 mice, shaker rat, PC degeneration in cats [35]. For all those models, further studies are needed to determine the similarity of induced tremors with those observed in ET patients.



**Fig. (2).** Tremor-generating mechanisms and related structures in the CNS. Harmaline directly acts upon coupled neurons of the inferior olive (ION). Cytosolic pores are composed of the neuron-specific connexin 36 (Cx36). Harmaline enhances neuronal synchrony and rhythmicity in the whole olivocerebellar system *via* the climbing fiber system. Deep cerebellar nuclei (DCN) project themselves back to the inferior olive *via* the inhibitory nucleo-olivary pathway. In GABA<sub>A</sub> receptor  $\alpha$ -1 subunit knockout mice, neuronal response to synaptic GABA is lost in cerebellar Purkinje cells, resulting in rhythmical activities. VIM (Ventral intermediate nucleus).

The GABA<sub>A</sub> receptor  $\alpha$ -1 subunit knockout mouse model [37] represents another rodent model of tremor, providing additional insight into the GABAergic mechanism involved in tremor genesis. Deletion of the GABA<sub>A</sub> receptor  $\alpha$ -1 subunit produces a tremor with postural and kinetic components similar to essential tremor. In these mice, the response to synaptic and exogenous GABA is lost in cerebellar Purkinje cells, but the brain remains morphologically intact. As in the harmaline model, the tremor can be inhibited by ethanol consumption. This tremor is genetic and persistent, an advantage, compared to short-lived chemical-induced tremors. Moreover, the efficacy of the few drugs used in the treatment of human ET is also observed in  $\alpha$ -1 knockout mice, lending further support to the model and possibly providing insight on ET-associated GABAergic dysfunction. However, this model should not be regarded as a genuine model of ET [38]. First, it has been shown that genetic mutations in the GABA<sub>A</sub> receptor  $\alpha$ -1 gene have



likely no significance in ET. Indeed, the frequencies of the GABRR1 (GABA receptor subtype rho1) genotypes and allelic variants do not differ between ET patients and control subjects [39]. Secondly, the onset of ET generally appears in elderly population and just occasionally during childhood, while tremor occurs early in development in these knockout mice. Finally, there are noticeable differences regarding the tremor frequency (knockout mouse: 16–22 Hz; ET: 4–12 Hz) [38]. Tremor frequency is known to be related in particular to the biomechanical features of limbs, such as inertia which is much higher in human.

As none of the animal models completely mimics the phenotype of human ET or recapitulates its histopathology, this clearly limits the prospects of discovering effective therapeutic agents. Also, to better understand the roles of the environment, new models are definitely needed. For instance, simple *in vitro* models, notably mini-brains, 3D lab-grown bundles of human brain cells that mimic the architecture of the cerebral cortex [40], could be adequate to assess neurotoxic agents and potential mechanisms leading to ET. This novel knowledge might help in devising new therapeutic options to identify neuroprotective measures for early-stage patients.

## **ET TREATMENT**

There is still no cure for ET and no therapy has shown an effect on the reduction of the natural progression of the disease. Current symptomatic treatments aim to reduce the involuntary movements as much as possible, providing relief and improving the quality of life. Current therapies are based on drugs and surgical procedures. Therapeutical options are selected according to the severity of tremor and side effects.

### **Pharmacotherapy**

All medications used to reduce tremor have initially been developed and approved for other indications. Unfortunately, the symptomatic drug benefit declines with time in all cases [41].

The first line therapy relies on propranolol and primidone [42]. Although propranolol is a well-known nonselective  $\beta$ -adrenergic receptor antagonist, the specific mechanism of its antitremor action has not been fully uncovered. The beneficial effect appears to be mainly due to blockade of peripheral beta-2 receptors on extrafusal muscle fibers and muscle spindles [43], although there may also be a synergistic CNS effect [44]. The daily dose varies from 60 to 800 mg/day with an average dose of 182.5 mg/day [45, 46]. There is no convincing evidence that doses higher than 320 mg/day may provide any additional benefit [46]. The proportion of responders varies from 50 to 70%, and the average tremor

reduction is about 50% when compared with placebo [47]. Efficacy of both conventional and long acting propranolol is established only for tremor affecting the upper extremities, while the head tremor response is quite limited [45, 48]. Side effects include worsening of a pre-existing asthma, sinus bradycardia and fatigue. The  $\beta$  adrenergic antagonists atenolol ( $\beta$ -1 selective) and sotalol (nonselective) are also used for tremor control; atenolol is proposed for patients with an increased risk of bronchospasms [49].

The antitremorogenic action of primidone, an anticonvulsant of the barbiturate class which is metabolized into the active metabolites phenobarbital and phenylethylmalonamide (PEMA), is not fully understood either. Primidone reduces high-frequency repetitive firing of neurons and modifies transmembrane sodium and calcium channels ion movements, a possible mechanism for both its anticonvulsant and antitremor activities [50]. The daily doses range from 50 to 1000 mg/day and the average dose is around 500 mg/day. Average tremor improvement is up to 75% reduction from the baseline, even though most studies reported approximately 50% improvement when compared with placebo [45, 51]. Primidone presents a high incidence of adverse effects, such as nausea, ataxia and confusion, ranging from 22 to 72% of patients, resulting in a dropout rate from therapeutic studies ranging from 20 to 30% [52, 53]. Primidone and propranolol may be used in combination to treat limb tremor when monotherapy does not sufficiently reduce tremor [42].

The second line therapy for ET includes alprazolam, gabapentin, topiramate and clozapine [42]. The benzodiazepine alprazolam is an allosteric modulator of the GABAergic neurotransmission, potentiating the influx of chloride ions. The resulting hyperpolarization of the cell membrane inhibits action potential firing [54]. Alprazolam at 0.125 to 3 mg/day reduces limb tremor intensity by 25 to 34%. Side effects are mild, with sedation and fatigue most common, reported in 50% of patients [55]. The risk of drug abuse should not be underestimated. Gabapentin, an anticonvulsant with a structure similar to GABA, probably interacts with auxiliary subunits of voltage-gated calcium channels [56]. According to some studies, gabapentin reduces tremor intensity by 77% when used as monotherapy in doses of 1,200 mg/day [57]. Topiramate presents complex mechanisms of anticonvulsant action, but it remains unknown which mechanism plays a role in tremor control. Its use is limited by the high incidence of adverse effects [58]. Clozapine, an atypical neuroleptic, is recommended only for refractory cases of limb tremor in ET due to the rare but serious risk of agranulocytosis [42, 59].

Ethanol decreases tremor severity in up to 50% of ET patients [60], but the side effects of sedation and intoxication clearly limit its use. However, this has led to

new trials for the treatment of ET, especially with long-chain alcohols such as 1-octanol and its metabolite octanoic acid (OA). 1-octanol was demonstrated to be safe and effective with excellent tolerability but the large volumes to be administered when formulated in capsules seem to limit further development as an effective treatment [61, 62]. Preclinical and early-stage clinical trial data indicate a promising efficacy and acceptable safety for OA, the 1-octanol active metabolite, with more favorable pharmacological properties for drug delivery. However, further studies on long-term safety and efficacy of OA are still needed [63, 64].

A future therapeutic option could be based on the administration of vanillin, a commonly used food additive and flavoring agent. Experimentally, vanillin reduces harmaline-induced tremors in rats. However, the mechanism of action remains unclear. A potent inhibitory effect on serotonin pathways in the brain has been suggested [65]. Trials in human are missing.

### **Surgical Treatment**

Thalamotomy causes a lesion in the ventral intermediate nucleus (VIM) of the thalamus. The target area is stereotactically localized. Micro-electrodes recordings are used to identify the typical pattern of discharges, confirming the location of the target. Neurostimulation with a macroelectrode can be applied in the awake patient during surgery to estimate tremor reduction and side effects. Unilateral thalamotomy reduces contralateral limb tremor in 80 to 90% of patients with ET [66, 67]. Bilateral thalamotomy is rarely performed nowadays because of common and often severe side effects [68, 69].

Deep brain stimulation of the thalamus (DBS) uses high frequency electrical stimulation exerted *via* an implanted electrode in order to modify the activity of the target area. The exact mechanisms by which DBS suppresses tremor are unknown, and postmortem examinations have not shown any permanent anatomic changes other than the electrode tract [70]. In most cases four electrodes, placed in VIM at a distance of 1.5 mm from each other, are connected to a pulse generator implanted in the chest wall. Electrode montage, voltage, pulse frequency and pulse width can be adjusted to optimize tremor control [71]. This flexibility in placing and adjusting the “functional lesion” is the main advantage of DBS as compared to thalamotomy which causes an irreversible lesion. Potential disadvantages of DBS include the higher cost and effort in programming and maintaining the device, in addition to dysfunction of the device related to cables. Following unilateral and bilateral DBS, mean tremor improvement reaches up to 60 to 90% on clinical rating scales as compared to baseline [72, 73].

Both techniques are invasive neurosurgical procedures. A long-term study of thalamotomy and DBS indicates that, although the benefits continue in most patients, a certain percentage of patients show a decline in response over time. This percentage of tremor recurrence has been reported as high as 35% in DBS [74]. The tremor recurrence can sometimes be effectively treated by changing the parameters of stimulation in patients who have undergone DBS but not in case of thalamotomy. A comparative study on 68 patients concludes that thalamic stimulation and thalamotomy are equally effective for the suppression of drug-resistant tremor, but thalamic stimulation has fewer adverse effects and results in a greater improvement of ET symptoms [66].

Gamma knife surgery (GK) is a non-invasive treatment based on radiation beams, from multiple angles, to an intracranial target based on anatomical imaging. In the case of ET, the target is the VIM. Alone, each beam is too weak to damage the healthy tissue through which it travels. However, the combined radiation is strong enough at the crossings of the beams to generate a local lesion. Several studies have found favorable results with gamma knife thalamotomy but the clinical improvement can take weeks to months. In follow-up studies, 92.1% of patients were entirely or nearly tremor-free postoperatively, and 88.2% remained tremor-free four years after the GK [75, 76]. Unfortunately delayed complications, such as complex movement disorders, have been reported [77].

Repetitive transcranial magnetic stimulation (rTMS) utilizes an electromagnet placed on the scalp to generate magnetic field pulses possessing roughly the strength of an MRI scan. The magnetic pulses stimulate an area of about 2.5 cm diameter on the surface of the brain. At low frequency (1 Hz), TMS induces small, sustained reductions in activity in the stimulated part of the brain. Low-frequency rTMS of the cerebellum can effectively modulate the cerebellar output, significantly improving total and specific (tremor, drawing, functional disability) scores, and reducing tremor amplitude [78]. However, a large clinical trial is still missing.

Another evolving technique of cerebellar neurostimulator is transcranial direct current stimulation (tDCS) [79], a powerful tool for the modulation of the cerebellar cortex excitability. The current (usually between 1 and 2.5 mAmp) is delivered at various sites, including the cerebellum and the frontal lobe [80]. Results obtained with the technique of transcranial alternating current stimulation (tACS) suggest that a single neural oscillator insures the temporal stability of ET tremor *versus* parkinsonian tremor frequency. There is a genuine hope that these techniques will be refined in the next years to reduce ET [81].

## BETA-CARBOLINES AND THEIR PUTATIVE MECHANISMS OF ACTION

The  $\beta$ CAs are a group of indole alkaloids that notably includes harmane, harmine and harmaline (Fig. 3).  $\beta$ CAs exhibit potent biological, psychopharmacological and toxicological activities. They occur naturally in plants, foods, and can be formed endogenously in mammals and humans [82].

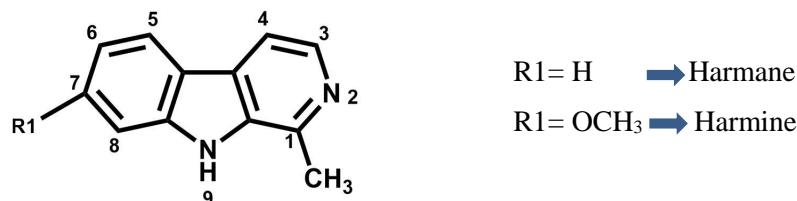
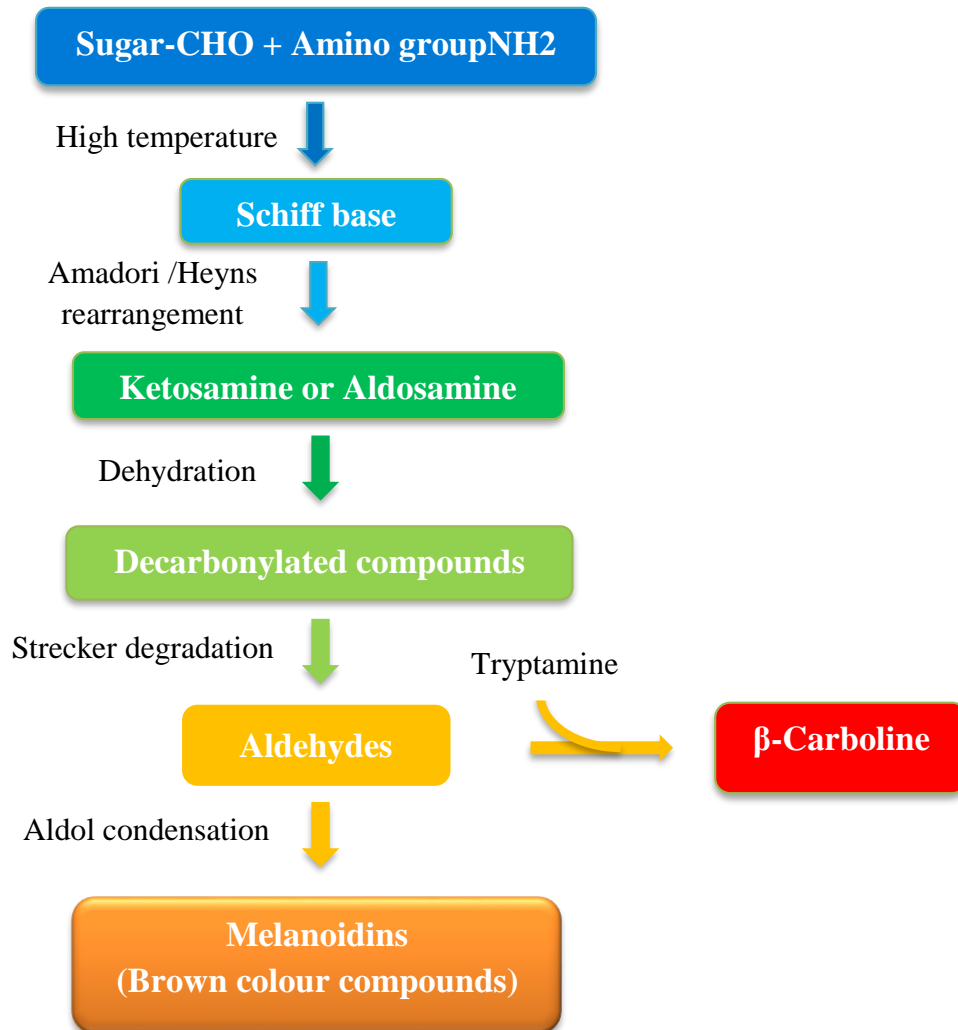


Fig. (3). Chemical structures of major  $\beta$ -carboline alkaloids ( $\beta$ CAs).

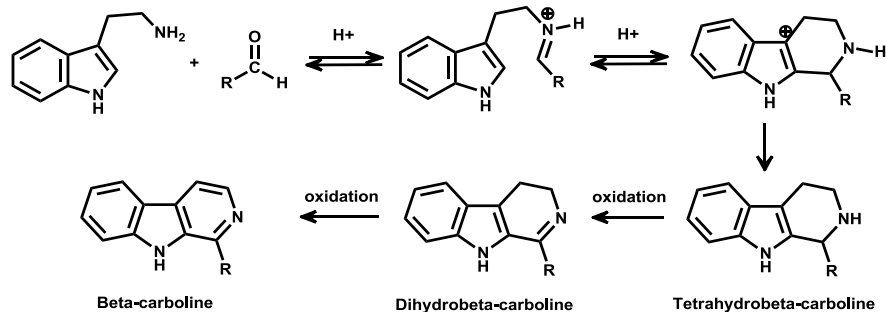
Structurally,  $\beta$ CAs are heterocyclic amines, consisting of a combination of five- and six-ringed cycles, containing 2 amine groups. There is some structural similarity with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which is commonly used to produce major toxin-induced animal models for Parkinson's disease [83]. Like MPTP, the  $\beta$ CAs are highly neurotoxic.

Harmane crosses the blood-brain barrier, through an active uptake mechanism, and concentrates in the brain [84]. Laboratory animals exposed to harmane and other heterocyclic amines develop an intense and generalized action tremor a few minutes after administration. Tremor resembles ET [85] and is accompanied by destruction of cerebellar tissues [86, 87]. The increased blood harmane concentrations in ET patients have clearly generated an interest in the pathogenesis. However, the mechanisms behind this observation are not clear. Increased chronic dietary intake and/or genetic-metabolic factors could be involved concomitantly [86, 88, 89]. Indeed, harmane is particularly abundant in meats, and its concentration is increased by certain cooking practices (*e.g.*, long cooking times, over-cooking) [82, 90], notably through the Maillard reaction, a succession of non-enzymatic glycation thermal reactions that provide the basis for the colors and aromas characteristic of cooked foods. This complex network of reactions, that begins by condensation of sugars with amino groups of proteins, peptides or amino acids, is followed by rearrangement into Amadori-/Heyns- and reductone-type products; these induce degradation of amino-acids to yield aldehydes that can condense with amines and cyclize through a Mannich-type reaction, eventually leading to the formation of various  $\beta$ CAs, including harmane (Fig. 4) [91, 92].



**Fig. (4).** Suggested pathway for the formation of  $\beta$ -carboline through Maillard reaction.

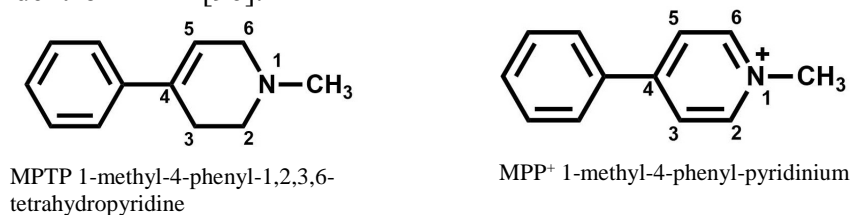
This alkaloid can also be endogenously generated in human tissues and brain through a Mannich-type reaction arising from aldehydes condensation with tryptamine derivatives (Fig. 5) [93].



**Fig. (5).** Pathway for endogenous synthesis of  $\beta$ CAs by condensation of endogenous tryptamine with aldehydes or keto-acids. Similar reaction could occur with tryptamine derivatives, such as serotonin.

### Bioactivation and Metabolization of Beta-Carbolines

MPTP Fig. (6) is well known to be neurotoxic. Its bioactivation to MPP<sup>+</sup> is carried out by the MAO<sub>B</sub> and MPP<sup>+</sup> is selectively absorbed into the nigrostriatal dopaminergic neurons *via* a dopamine transporter (DAT). Given some structural analogy with MPTP, the potential neurotoxic effects of  $\beta$ CAs were investigated [94].  $\beta$ CAs are usually less toxic than MPTP/MPP<sup>+</sup>. As pointed out above,  $\beta$ CAs occur naturally, have been detected in human brain and might contribute to the degeneration of dopaminergic neurons during chronic exposure [95].  $\beta$ CAs are also transported by DAT, but with lower efficiency than dopamine. They present enhanced cytotoxicity in DAT-expressing cells. Nevertheless, the low affinities of  $\beta$ CAs to DAT suggest other absorption pathways of neurotoxic  $\beta$ CA<sup>+</sup>s, independent of DAT [96].



**Fig. (6).** Chemical structure of MPTP and MPP<sup>+</sup>.

The neurotoxicity of endogenous and exogenous  $\beta$ CAs is then probably affected by several factors, including their bioavailability, their toxic potential, their bioactivation/metabolism and their affinity for DAT.

The bioactivation of  $\beta$ CAs by N-methyltransferases (NMT) into the cationic neurotoxicants 2-ME- $\beta$ CA<sup>+</sup>s and 2,9-diME- $\beta$ CA<sup>+</sup>s is important for their relocalization to the brain and neurotoxicity [97]. Although the N-methylation

may occur on both nitrogens, the methylation of the indole nitrogen appears to be the rate-limiting step in the development of toxicity [98]. Toxicity increases for  $\beta$ CAs methoxylated on the indole ring [95, 97].

Oxidative metabolism is another route for beta-carboline bioactivation [93, 99], through a reaction catalyzed by heme peroxidases, including myeloperoxidase and lactoperoxidase; these could be key catalysts for the bioactivation of endogenous and naturally occurring N-methyl-tetrahydro- $\beta$ CAs [93, 99].

Metabolisation of  $\beta$ CAs in the liver and peripheral tissues by P450 enzymes (CYP1A, CYP1A2, CYP2C9, CYP2C19 and/or CYP2D6, depending on the  $\beta$ CA) may serve as detoxification routes, leading to hydroxylated  $\beta$ CAs, suggesting a possible role for cytochromes in protecting from this neurotoxin [100].

### **Beta-Carbolines: Neurotoxin or Neuroprotective?**

Neurotoxicity of  $\beta$ CAs depends on the dose. High or chronic doses trigger neurotoxicity [98]. By contrast, low doses may increase dopamine levels and perhaps even present protective properties [101].

To achieve neuroprotection, both enzymes MAO<sub>A</sub> and MAO<sub>B</sub> should be inhibited to a certain level. This inhibition decreases the production of detrimental reactive oxygen species (ROS), a primary factor in neurodegeneration.  $\beta$ CAs can inhibit MAOs. Interestingly,  $\beta$ CAs (norharman and harman) have been identified in cigarette smoke [102]. This inhibition may explain the reduced risk of Parkinson's disease observed in smokers [103]. Nevertheless, it should be emphasized that, although neurodegenerative diseases share many pathological features like oxidative stress, iron accumulation, excitotoxicity and elevated ROS production [104], the neuroprotective action of tobacco smoke cannot be generalized to other neurodegenerative diseases, for example Alzheimer's disease [105].

An example of protective effects is the administration of harmine to a rat model of global cerebral ischemia. Harmine attenuates cerebral infarct volume and decreases neuronal death. It also causes a significant elevation of the glutamate transporter-1 (GLT-1) mRNA/protein and a remarkable attenuation of astrocyte activation [106]. In addition, harmine induces up-regulation of GLT-1, a neuroprotective effects in a rat model of amyotrophic lateral sclerosis disease [107]. GLT-1 dysfunction has been shown in the pathogenesis of multiple neurological disorders, including stroke and Alzheimer's disease. These findings certainly warrant further studies.

Moreover, calcium has been incriminated in the pathogenesis of neurodegeneration. Since GABA pathways are involved in the control of calcium

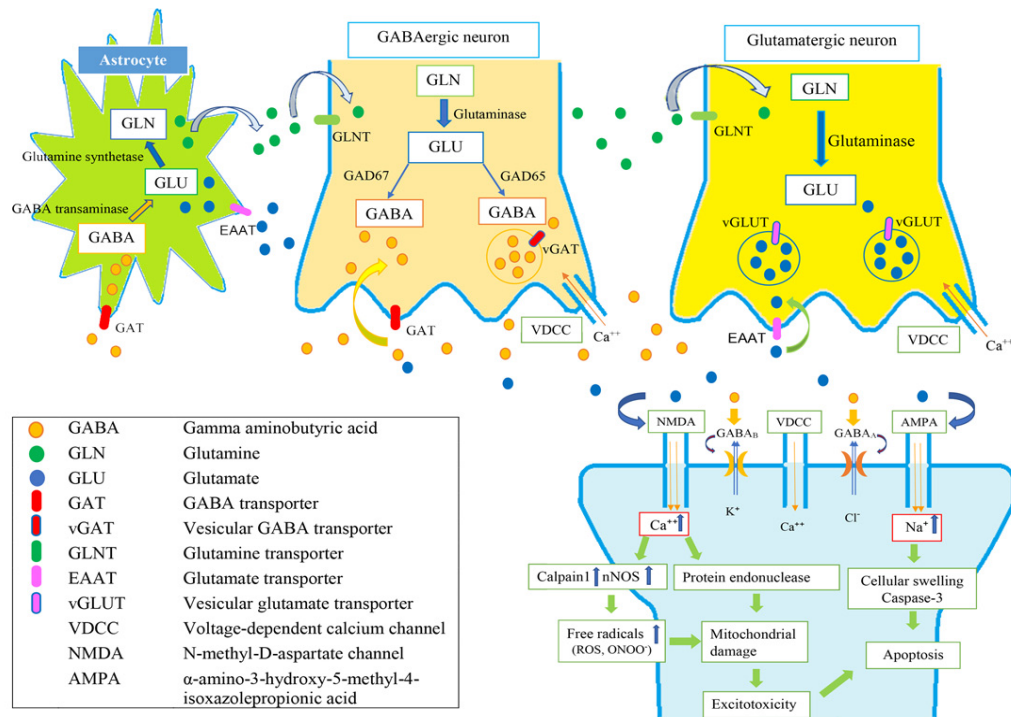


influx, directly *via* GABAergic receptors and indirectly *via* astrocytes and glial networks [108], the modulation of GABA transmission is potentially interesting when a neuroprotection is envisioned. It would be worth studying the putative relationship with  $\beta$ CAs, since the hypothesis of an intra-cellular calcium imbalance may apply to all human degenerative processes [109]. Also, the relationships between  $\beta$ CAs and L-glutamic acid decarboxylases isoforms GAD67 and GAD65 (molecular weights of 67 and 65 kDa, respectively) should be further investigated, since these isoforms are responsible for regulating the biosynthesis of GABA and its packaging into synaptic vesicles [110]. Very interestingly, GAD inhibition triggers a NMDA-mediated neuronal degeneration [111]. Recent reports highlight that MDMA (3,4-methylene-di-oxy- methamphetamine) reduces GAD67 in the hippocampus, with an increase in seizure susceptibility involving glutamate receptor activation [112]. This confirms the importance of GAD67 in the homeostasy of the balance GABA/glutamate. Harmaline increases the extra-cellular concentrations of glutamate in cerebellar nuclei and impairs the NMDA-mediated regulation of glutamate (Fig. 7) [113]. As discussed here over, ET is highly responsive to alcohol, benzodiazepines and barbiturates, which all facilitate inhibitory neurotransmission by binding to the GABA<sub>A</sub> receptor in the brain [29]; a pharmacological correction of GABA dysfunction thus has a potential for ET therapy.

## **NEUROPROTECTIVE PROPERTIES OF DIETARY PHYTO-CHEMICALS AND HERBAL THERAPIES IN ET?**

### **A Novel and Under Recognized Avenue for Research**

The search for effective treatments of ET is on-going; given the high worldwide prevalence of the disease, it is conceivable that some plants used in traditional medicines may be effective and yield clues to developing new pharmacotherapies. In neurodegenerative disorders, in addition to the importance of neurotrophins levels, the role of oxidative stress and inflammation factors has been proven [114]. Both dietary phytochemicals (such as phenolic acids, catechins, flavonoids, anthocyanins, stilbenoids, curcuminoids) and herbal therapies have a strong potential neuroprotective effect. From the extensive list of herbal medicines proposed to treat neurological diseases [115], some are noteworthy; but, most often, their mechanisms of action have not been determined and clinical studies are lacking.



**Fig. (7).** Illustration of an astrocyte (green), a pre-synaptic Gabaergic (brown) neuron, a pre-synaptic Glutamatergic neuron (yellow) and a post-synaptic neuron (blue). Overstimulation of glutamatergic receptors results in an excitotoxic cascade triggered by an excess of calcium entry at the post-synaptic site.

### Plants Well-Known for Neuroprotective Effects

Wild Syrian rue (*Peganum harmala* L.) seeds, bark, and root have demonstrated different pharmacological and therapeutic effects in the fields of cardiovascular, gastrointestinal, endocrine, cancer, pain, diabetes, respiratory, antimicrobial, anti-inflammatory, febrifuge and, mainly, nervous diseases [116]. The most important phytochemicals of the different parts of the plant are beta-carboline..... [117], especially harmalol, harmaline and harmine, and quinazoline [118] alkaloids. As discussed in the previous section, it is debated whether βCAs are neurotoxic or neuroprotective; this probably depends on their structural features, dose and duration of use. βCAs are inhibitors of MAO and interact with CNS receptors of opioids, dopamine, GABA, 5-hydroxytryptamine, and benzodiazepines, which may explain their numerous pharmacological effects [116].

The whole plant of *Bacopa monnieri* (L.) Wettst., traditionally used in India for longevity and cognitive enhancement is certainly one of the most promising herbal medicines in the neurology field. Neuroprotective effects of its extracts

include antioxidant/neuroprotection, acetylcholinesterase inhibition, choline acetyltransferase activation,  $\beta$ -amyloid reduction, increased cerebral blood flow, and monoamine potentiation and modulation. The active constituents, bacosides, triterpenoid saponins with at least twelve known analogs [119], are heavily metabolized; a major metabolite, ebeline lactone could be the main neuroprotective agent [120]

The leaves of *Ginkgo biloba* L. harbor two major classes of active components, flavonoids and ginkgolides, known for their neuroprotective properties through different possible mechanism of action, PAF antagonism, ROS and NO scavenging, interaction with neurotransmitters and induction of growth factors [121, 122].

In the Ayurveda remedy, *mandukaparni* (*Centella asiatica* (L.) Urb.), the major constituents are saponins (medacoside, asiaticoside, medacassoside, based on asiatic acid) and polyphenols [123]. The chloroform: methanolic extract showed neuroprotective efficacy due to free radical scavenging by the polyphenols and flavonoids [124].

*Rubia cordifolia* L., *Fagonia cretica* L. and *Tinospora cordifolia* (Willd.) Miers (a synonym of *Tinospora sinensis* (Lour.) Merr.) have been reported to be a rich source of antioxidants [125 - 127]. They act by reducing oxidant levels through direct scavenging to protect cells from free radicals generated during immune activation, which explains their properties as antioxidant and anti-inflammatory [128].

### **Phytochemicals Reported for Neuroprotective Effects**

Many phytochemicals have been reported to exert neuroprotective effects [129], modulating some changes observed in neurodegenerative disorders.

Dietary polyphenolic compounds (phenolic acids, flavonoids,...) have shown a high efficacy as antioxidant and neuroprotectors [130] and many studies have reviewed their efficacy against neuroinflammation and apoptosis [131]. For example, grape polyphenols modified by fermentation, as found in red wine, are protective against neuronal death induced by 3-morpholinopyridone (SIN-1) in a dopaminergic cell line [132].

Studies indicate that, in addition to their antioxidant activity, catechins, the phenolic compounds of green tea, are capable to modulate the signal transduction pathways that can exert cell-survival and anti-inflammatory actions [133].

As neuroprotective agent, however, polyphenols such as flavonoids must cross the

brain blood barrier (BBB) to protect vulnerable neurons [134]. Experimental data suggest that intact anthocyanins and/or their metabolites do enter the brain of rats [135] and pigs [136] fed diets supplemented with anthocyanins-rich extracts; in cellular models, these were found to enhance the mitochondrial function, a possible mechanism for neuroprotection [137].

Stilbenoids consist in a family of resveratrol derivatives. Resveratrol modulates multiple mechanisms important in neurodegenerative diseases, notably protecting dopaminergic neurons against metabolic and oxidative insults, in models relevant to Parkinson's and Alzheimer's diseases [138].

Curcumin has shown potent antioxidant, anti-inflammatory and anti-protein-aggregate activities [139] but poor BBB penetration. Nevertheless, many studies have investigated the role of curcumin in neurodegenerative disorders, indicating that curcumin may stop death cascades in neurodegenerative disorders, preventing the death of cells from inflammation and oxidative stress and reducing the aggregation of  $\alpha$ -synuclein, a major component of the Lewy body lesions [140]. Various curcuminoids are being investigated for enhanced BBB penetration [141].

Given the prevailing hypothesis of a slow progressive neurodegenerative mechanism in ET, there is a definite need to explore whether a genuine neuroprotection would occur with dietary herbs and/or medicinal plants. A chronic administration in a cohort of patients could be envisioned, comparing with a matched control group.

## CONCLUSION

ET is a highly prevalent neurological disorder affecting in particular the elderly, impairing the quality of life and whose pathogenesis remains poorly understood. ET is clinically heterogeneous, combining motor features with various cognitive and psychiatric signs. Both genetic and environmental factors probably contribute to the mechanisms of this slowly progressive neurodegenerative disease. Oxidative stress and inflammation factors leading to overactivation of glutamatergic pathways are suspected to explain the neurodegeneration process occurring in the brain, especially at the level of Purkinje neurons in the cerebellar cortex. Several studies point out the probable implication of dietary  $\beta$ CAs, formed in some overcooked foods especially *via* the Maillard reaction, in the cascade of events leading to tremor. The current lack of satisfying animal models impacts on the development of effective therapeutic options and we still miss effective strategies of prevention. Surprisingly, none of the therapies currently administered (drugs, surgical procedures) in patients target a neuroprotective effect. Since both dietary phytochemicals and herbal therapies may have a strong potential neuroprotective action, we suggest devising studies testing the hypothesis that

efficient herbs will yield important clues to develop novel pharmacotherapies. Furthermore, we have discussed the dysfunction of GABA pathways and we have stressed the importance of GAD enzymes. Those enzymes might be a candidate target to restore the GABA/Glutamate balance. The era of neuroprotection is now emerging for one of the commonest movement disorders.

## **ABBREVIATIONS**

<b>ADL</b>	Activities of Daily Living
<b>AMPA</b>	$\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
<b>BBB</b>	Brain Blood Barrier
<b><math>\beta</math>CA</b>	Beta Carboline Alkaloid
<b>CNS</b>	Central Nervous System
<b>DAT</b>	Dopamine Transporter
<b>DBS</b>	Deep Brain Stimulation
<b>DCN</b>	Deep Cerebellar Nuclei
<b>ET</b>	Essential Tremor
<b>EAAT</b>	Excitatory Amino Acid Transporter
<b>fMRI</b>	Functional Magnetic Resonance Imaging
<b>GABA</b>	Gamma Aminobutyric Acid
<b>GABA<sub>A</sub></b>	Gamma Aminobutyric Acid A
<b>GABA<sub>B</sub></b>	Gamma Aminobutyric Acid B
<b>GABRR1</b>	GABA Receptor Subtype Rho1
<b>GAD</b>	Glutamic Acid Decarboxylase
<b>GAT</b>	GABA Transporter
<b>GK</b>	Gamma Knife Surgery
<b>GLN</b>	Glutamine
<b>GLNT</b>	Glutamine Transporter
<b>GLT</b>	Glutamate Transporter
<b>GLU</b>	Glutamate
<b>HCA</b>	Heterocyclic Amine
<b>ION</b>	Inferior Olivary Nucleus
<b>MAO<sub>A</sub></b>	Monoamine Oxidase A
<b>MAO<sub>B</sub></b>	Monoamine Oxidase B
<b>MDMA</b>	3,4-Methylenedioxy-methamphetamine
<b>MEG</b>	Magneto Encephalography
<b>MPTP</b>	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

<b>MPP+</b>	1-methyl-4-phenyl-pyridinium
<b>MRI</b>	Magnetic Resonance Imaging
<b>mRNA</b>	Messenger Ribonucleic Acid
<b>N-MeTH-<math>\beta</math>C</b>	N-methyltetrahydrobetacarboline
<b>NMDA</b>	N-methyl-D-Aspartate Channel
<b>NMT</b>	N-methyltransferases
<b>NO</b>	Nitric Oxide
<b>OA</b>	Octanoic Acid
<b>PAF</b>	Platelet-Activating Factor
<b>PEMA</b>	Phenylethylmalonamide
<b>PET</b>	Positron Emission Tomography
<b>ROS</b>	Reactive Oxygen Species
<b>SIN-1</b>	3-morpholinopyridone
<b>rTMS</b>	Repetitive Transcranial Magnetic Stimulation
<b>tACS</b>	Transcranial Alternating Current Stimulation
<b>tDCS</b>	Transcranial Direct Current Stimulation
<b>VDCC</b>	Voltage-Dependent Calcium Channel
<b>vGAT</b>	Vesicular GABA Transporter
<b>vGLUT</b>	Vesicular Glutamate Transporter
<b>VIM</b>	Ventral Intermediate Nucleus

**CONSENT FOR PUBLICATION**

Not applicable.

**CONFLICT OF INTEREST**

The authors confirm that they have no conflict of interest to declare for this publication.

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