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Catalepsy, A Scientific Model For Exploring Unani Herbs Having Possible Specificity for Different Neurotransmitters: A Review.

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ABSTRACT

One of the challenges faced by scientific community is that of adverse and deterioting side effects of psychotropic agents, which are popularly known as neuroleptic induced extrapyramidal adverse effects. Neuroleptic induced movement disorders pose a significant burden to patients, often resulting in non-adherence, disease relapse, and decreased quality of life. Evidence indicates that drugs which potentiate or attenuate neuroleptic induced catalepsy in rodents might aggravate or reduce the extrapyramidal signs respectively in human beings. It is being appreciated that many plant drugs can be explored for their protective nature against such adverse and toxic effects on account of their ascribed effects.

Keywords: Neuroleptic, Catalepsy, Unani medicine, Extrapyramidal, Dopamine

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INTRODUCTION

Catalepsy is a nervous condition characterized by muscular rigidity and fixity of posture regardless of external stimuli, as well as decreased sensitivity to pain. Catalepsy is also a term used by hypnotists to refer to the state of making a hypnotized subject's arm, leg or back rigid.[1,2] Catalepsy may be defined as a condition in which person maintains the body position into which they are placed and is observed in severe cases of catatonic schizophrenia. It is also called as waxy flexibility, cerea flexibilitas.[3] During the attack of catalepsy the psychomotor disturbances are very much prominent as seen by posturing, negativism, rigidity or common automatism. Extrapyramidal disorders involve those parts of the motor system which are not directly "pyramidal", that is not involving the corticospinal tracts (upper motor neurons). It includes the basal ganglion formed by six-paired nuclei, i.e. caudate nucleus, putamen, globus pallidus (pallidum), nucleus accumbens, subthalmic nucleus and substantia nigra. The normal function of extrapyramidal system is sustained posture, resting tone and patterned movements. In addition to catalepsy, the various disorders which are observed due to any pathological condition imposed on basal ganglion due to some internal organic disorder or by some external cause includes Parkinsonian syndromes, chorea, hemiballismus, athetosis, dystonia,tardive dyskinesia, catatonic schizophrenia, akathisia, Parkinson's disease. Disturbed motor activity involving the extrapyramidal system is also seen in a number of physical disorders .e.g., hypothyroidism, Addison's disease.[1,2] Catalepsy is a symptom of certain nervous disorders or conditions such as Parkinson's disease and epilepsy.[4] It can be caused by treatment of schizophrenia with anti psychotics, such as haloperidol. In some cases, isolated cataleptic instances can also be precipitated by extreme emotional shock. [5] The catalepsy is dominated by prominent psychomotor disturbances which involve posturing, negativism, rigidity, waxy flexibility, command automatism. Normally in a person motor behaviour is finely coordinated, purposeful and adaptive, and necessary activities are usually carried out efficiently. Neuroleptic induced movement disorders constitute a worldwide problem in the treatment of psychiatric disorders because of limited affordability of atypical antipsychotic drugs, their high cost and atypical antipsychotics causing extrapyramidal symptoms. The prevalence rates of neuroleptic induced movement disorders defined by DSM-IVR (Diagnostic and Statistical Manual of Mental Disorders , Fourth Edition ,revised) criteria are 29%-74%, of which 9%-35% consists of neuroleptic induced akathisia, 9%-36% consists of neuroleptic induced tardive dyskinesia.[6] In spite of the increasing use of second generation antipsychotics, patients still suffer from

neuroleptic induced movement disorders. In the initial years of introduction of neuroleptics, adverse movement effects were considered to be an indicator of antipsychotic actions, but today they are seen as burdening and stigmatizing phenomenon that should be avoided by careful choice of treatment.[7] Hence, in order to minimize the undesired extrapyramidal effects of these antipsychotics, a need arises to scientifically evaluate traditional drugs, which can be used as an alternative to mainstream drugs or as an adjuvant with the conventional antipsychotics. It is being appreciated that many plant drugs can be used to protect such toxic effects on account of their ascribed effects which have also been evidenced in some of the studies like effect of Tulsi (*Ocimum sanctum* Linn*)*, *Ficus bengalensis* Linn, Toot (*Morus alba* Linn*)*, Aamla (*Embelica officinalis* Linn*)*, *Ginko biloba* etc. on haloperidol-induced catalepsy in mice**.**[8] Unani system of medicine also has got several drugs / drug therapies which are claimed to be effective in catalepsy without such side effects. Unani medicine has well charted therapeutic plan to alleviate the pathology of such condition, therefore, the drugs which are helpful in combating the disorders similar to the catalepsy, need to be evaluated for their efficacy in such conditions. The Unani system of medicine offers a number of drugs useful in the management of neurological and related disorders. These drugs are being used successfully since hundreds of years. There are several single drugs, such as, Aftimoon (*Cuscuta reflexa* Roxb), Ghariqoon (*Agaricus alba* Linn), Bisfaij (*Polypodium vulgare* Linn), Ustakhudoos (*Lavandula stoecha Polypodium vulgare* Linn), Halela Siyah (*Terminalia chebula* Retz), Badranjboya (*Melissa parviflora* Benth), Bekhe Kasni (*Cichorium intybus* Linn), Parsiaoshan (*Adiantum capillusveneris* Linn)), Gule Neelofar (*Nymphaea alba* Linn)), Khayaar Shambar (*Cassia fistula* Linn*)*, Sana makki (*Cassia angustifolia* Vahl) which have been described to possess antipsychotic activity.[9] These drugs either remove the excessive and morbid *Sauda* (black bile)or improve its quality. These are used to improve the neurological disorders, because derangement in *Sauda* (black bile) is considered the main causative factor of these disorders. All the above mentioned drugs have ability to improve psychiatric disorders by removing or inactivating the morbid matter (black bile), but these drugs have not been scientifically evaluated for their ascribed effects and no data is available which validate their efficacy and safety.[10,11,12]

Pathophysiology of Catalepsy:

The data obtained both in humans and laboratory animals, point to the blockade of a large number of the striatal dopamine D2 receptors by neuroleptics as a primary cause of neuroleptic induced extrapyramidal side effects. Consequently, catalepsy test became an assay for

antipsychotic action. Strict correlation was demonstrated between strength of cataleptogenic action of a neuroleptic and its antipsychotic efficacy.[13] Extrapyramidal side effects proved to belong to the most deleterious neuroleptic-induced effects. They generally appear early in the treatment (most often within the first several days, and not later than after 2 months). Parkinsonism is such "early" complication, characterized by the symptoms resembling those observed in idiopathic Parkinson's disease: akinesia (immobility), bradykinesia (slow movements), muscular rigidity and tremor. Besides Parkinsonism, akathisia (restlessness) and acute dystonia (strong spasm of tongue, face, neck and back muscles leading to abnormal, twisted body posture) [14,15] may occur in this period as well. These extrapyramidal side effects are caused mainly by so called typical neuroleptics, known since many years, such as haloperidol, fluphenazine or chlorpromazine. It is a general rule that a neuroleptic which induces strong early disturbances causes strong late onset effects, and conversely, the drug causing only weak early side effects evokes also weak late onset symptoms.[15] It appeared at that time that extrapyramidal side effects were inseparably connected with therapeutic action of these drugs, so they could be considered as their indicators. Consequently, catalepsy test became an assay for antipsychotic action. Catalepsy, a behavioural immobility associated with varying degrees of enhanced muscular rigidity, serves as an experimental animal model of Parkinsonism.[16] Catalepsy induced by haloperidol represents a useful model of Parkinson's disease and has been used for detecting antipsychotic drugs with extrapyramidal side effect liability and for evaluating the utility of antidepressant drugs for the treatment of depression associated with Parkinson's disease.[17,18,19,20] Catalepsy is a behavioural state observed in animals in which there is a decrease in motor activity, though the animals remain fully alert and perceptive. Munkvad et al. defined catalepsy as "a state of apparent sedation in which the animals do not respond when placed in unnatural positions, maintaining these for considerable length of time with well preserved righting reflex and perception".[21] The importance of catalepsy lies in the fact that there exists a reasonably good correlation between the therapeutic efficacy of anti- Parkinson drugs and their anti-cataleptic effects. Obviously, experimental catalepsy can serve as a faithful index for the assessment of extrapyramidal syndromes in human beings, and has been frequently deployed as a convenient laboratory model for Parkinson's disease. Besides dopamine receptor blockade and catecholamine depletion, other neurochemical hypothesis have been proposed for the development of catalepsy such as striatonigral GABAergic, cholinergic, glutamate and serotonergic etc.[22,23] Extrapyramidal effects of most clinically used antipsychotic drugs are prominent , a great deal of interest has centered on the actions of these drugs in the basal ganglia,

notably the caudate nucleus, putamen, global pallidus, and allied nuclei, which play a crucial role in the control of posture and extrapyramidal aspects of movement. One of the powerful modulators of this network is the neurotransmitter dopamine. Dopaminergic input to this network comes from the substantia niagra pars compacta (SNc) and predominantly impacts neurons in the putamen, in the case of the motor sub cortical circuits, but may also affect 45GPi and thalamic neurons directly given observations of dopaminergic receptors in these nuclei.[1] Dopamine can have either an inhibitory or excitatory effect on striatal neurons depending on the receptor subtype. D1 receptors result in an excitatory effect while D2 receptors result in inhibitory effect. The net effect of dopaminergic input to the striatum is to reduce basal ganglia output and subsequently disinhibit thalamocortical activity. Furthermore, dopaminergic activity also has the net effect of facilitating activity through the direct pathway over the indirect pathway.[8] Dopamine contributes significantly to the pathophysiology of psychiatric disorders. Reduced neurotransmission in the mesolimbic dopamine system

may sustain some of the symptoms of depressive conditions such as dysthymia[24] and melancholic depression.[25] Since dopamine plays a crucial role in controlling incentive, motivation and reward, its deficiency at the mesolimbic level induces syndromes characterized by anhedonia, low energy, lack of motivation and psychomotor slowing.[26] Dopamine hypo activity, a relevant factor in the pathogenesis of psychomotor retardation, is considered essential for movement control also. It has been observed that depressed subjects with psychomotor retardation have a marked decrease in homovanillic acid (HVA) a major dopamine metabolite in cerebral fluid, indicate, a diminished dopamine turnover at the postsynaptic level.[27,28] It seems that dysfunction in dopaminergic transmission is due to decreased density of D2/D3 dopamine post synaptic receptors in the nucleus accumbens. Comparison of the affinity of different neuroleptics to dopamine D2 receptors showed that the drugs, which caused the strongest extrapyramidal side effects (haloperidol, fluphenazine, benperidol, spiperone or chlorpromazine) bound to dopamine D2 receptors with very high affinity, [29] Contrariwise to atypical neuroleptics. Therefore, it seems that strength of neuroleptic- induced extrapyramidal disturbances depend most of all on their binding to D2 receptors. Neuroleptic induced extrapyramidal side effects is connected with the blockade of dopamine D2 receptors in the striatum, since it was shown in many animal experiments that the main difference between typical and atypical neuroleptics lay in strong effect on this structure. Brain imaging in humans after treatment with neuroleptics are decisive for understanding of therapeutic mechanisms underlying drug actions which include positron emission tomography (PET) and single photon emission computed tomography

(SPECT). These experiments revealed that neuroleptics such as haloperidol at the doses commonly used in clinical practice and causing extrapyramidal side effects, occupied more than 80% of D2 receptors. [30,31,32,33,34] As the main target of the action of different neuroleptics is Dopamine D2, its blockade changes the activity of many neuronal pathways, transmitting impulses from the striatum, through numerous relay stations (brain structures and spinal cord) to effectors, which are muscles in case of extrapyramidal disturbances. However, similarity of the changes observed after haloperidol administration and in Parkinson's disease, namely disturbance of functional balance between striatal efferent pathways, resulting ultimately in the stimulation of the pathways leaving the basal ganglia (nigrothalamic pathway), substantiates their significant role in neuroleptic-induced Parkinsonism. Since all neuroleptics elicited Parkinsonian symptoms, the hypothesis was propounded that they were connected with hypo function of dopaminergic system.[32] In addition; positive correlation was demonstrated between affinity of different neuroleptics to D2 receptor and their clinical efficacy .[13] In the initial years of introduction of neuroleptics, adverse movement effects were considered to be an indicator of antipsychotic actions, but today they are seen as burdening and stigmatizing phenomenon that should be avoided by careful choice of treatment.[7] Hence, in order to minimize the undesired extrapyramidal effects of these antipsychotics, a need arises to scientifically evaluate traditional drugs, which can be used as alternative to mainstream drugs or as an adjuvant with the conventional antipsychotics. It is being appreciated that many plant drugs can be used to protect such toxic effects on account of their ascribed effects which have also been evidenced in some of the studies like effect of Tulsi (*Ocimum sanctum* Linn*), Ficus bengalensis* Linn, Toot (*Morus alba* Linn*),* Aamla (*Embelica officinalis* Linn*), Ginko biloba* etc. on haloperidol-induced catalepsy in mice**.**[13] Unani system of medicine also has got several drugs / drug therapies which are claimed to be effective in catalepsy without such side effects. Unani medicine has well charted therapeutic plan to alleviate the pathology of such condition, therefore, the drugs which are helpful in combating the disorders similar to the catalepsy, need to be evaluated for their efficacy in such conditions. The Unani system of medicine offers a number of drugs useful in the management of psychiatric and related disorders. These drugs are being used successfully since hundreds of years. There are several *mufrad* drugs, such as, Aftimoon (*Cuscuta reflexa* Roxb), Ghariqoon (*Agaricus alba* Linn), Bisfaij (*Polypodium vulgare* Linn), Ustakhudoos (*Lavandula stoecha Polypodium vulgare* Linn), Halela Siyah (*Terminalia chebula* Retz), Badranjboya (*Melissa parviflora* Benth), Bekhe Kasni (*Cichorium intybus* Linn), Parsiaoshan (*Adiantum capillusveneris* Linn)), Gule Neelofar (*Nymphaea alba* Linn)), Khayaar Shambar (*Cassia fistula*

Linn*)*, Sana makki (*Cassia angustifolia* Vahl) These drugs either remove the excessive and morbid black bile or improve its quality. These are used to improve the psychiatric disorders, because derangement in *Sauda* (black bile) is considered the main causative factor of these disorders. All the above mentioned drugs have ability to improve psychiatric disorders by removing or inactivating the morbid matter (black bile), but these drugs have not been scientifically evaluated for their ascribed effects and no data is available which validate their efficacy and safety. Assessment of catalepsy by 'standard bar test' has been proved in various studies to be a 'good validity model' for assessment of anti cataleptic effect. [10, 12,35,36 ,37,38,] Catalepsy induced by neuroleptics and its assessment by 'standard bar test' is of interest, because of its similarity to symptoms of such human disorders as Parkinsonism, catatonic schizophrenia and brain damage involving parts of the basal ganglia. In addition, catalepsy is one of the behavioral tools mostly used by neuroscientists to study the behavioral mechanism of neurochemical systems. The behavioral catalepsy test can employ any of several different types of apparatus, but the most common by far is the "bar test," originally described by Kuschinsky and Hornykiewicz (1972).[38]

CONCLUSION:

The study will have a huge implication in the clinical management of the catatonic states. As of now, no drug has been developed which does not compromise with the other functional states and is invariably having serious side effects. The conventional therapy is also costly and most of the times, compliance issues also come up with the use of these drugs. So, it is a step towards exploring different herbs and the development of cost effective and safe drug for health care.The catalepsy test can be designed to evaluate the test drugs on single dose (acute study) and multiple dose (chronic study) so that the Unani herbs having possible specificity for different neurotransmitters may be evaluated in time dependent manner. Multiple doses of the test drugs can be chosen to evaluate dose dependent activity of the drugs.

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