

Review: *Tinospora cordifolia* in the Treatment of Depression

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Abstract:

Depression is a complex psychiatric disorder characterized by depressed mood, anhedonia, loss of energy and low self esteem. Nitric oxide (NO) is the smallest biologically active molecules which plays an important role in the intracellular signaling. NO negatively controls the levels of 5-HT. Inhibition of NO synthases (NOS) which are responsible for the production of NO; may exert antidepressants like action. Thus, NO is involved in the pathogenesis of depression and the agents which suppress the NO production exerts antidepressants like effect. *Tinospora cordifolia* commonly named as "Guduchi" belonging to family Menispermaceae; has been reported of its strong free radical scavenging properties against superoxide anion (O_2^-), hydroxyl radicals (OH), NO, and peroxynitrite anion ($ONOO^-$). Thus the aim of the present manuscript is to demonstrate the role of NO in depression and how *Tinospora cordifolia* exerts beneficial effects in the patients of depression.

Keywords: Depression, Nitric Oxide, *Tinospora cordifolia*.

INTRODUCTION

Depression is a complex psychiatric disorder characterized by depressed mood, anhedonia, loss of energy and low self esteem. Dysregulation of monoaminergic neurotransmitters found to be involved in the etiology of depression. ^[1] The clinical characteristics of depression include mood changes, hopelessness, depressive episode, psychomotor retardation etc. ^[2] Stress, is an important risk factor for depression and the acute stressful life events have been found to be responsible for the onset of depression. ^[3] Serotonin (5-HT) and norepinephrine are primarily involved in regulation of mood and emotions and the alteration in the levels and transmission of these neurotransmitters is responsible for depression. Thus the lower levels of the 5-HT levels is linked with depression or may increase the vulnerability to depression. ^[4] Therefore the drugs which correct the alterations in the 5-HT signaling will be useful in the treatment of depression. SSRIs have been used in the treatment of the depression from the very long time, these drugs offers various advantages over the various other categories of the drugs used for the treatment of depression. But the treatment with the SSRIs increases the risk of suicides in the patients suffering from depression. Therefore there is a constant need

of newer and safer antidepressants which are free from these life threatening adverse effects.

Nitric oxide (NO) is the smallest biologically active molecules which plays an important role in the intracellular signaling. NO serves as an unconventional messenger molecule in the nervous systems implicated in various cellular processes. ^[5] NO is synthesized from L-arginine by nitric oxide synthases (NOS). NO is produced by three cell-specific NOS isoforms that are classified according to the tissue or cell type in which they were first found: neuronal nitric oxide synthase (nNOS, NOS-I or Type I), expressed in most brain regions by small populations of neurons, typically GABAergic and also in skeletal, cardiac and smooth muscles; inducible nitric oxide synthase (iNOS, NOS-II or Type II), initially identified in macrophages and glia; and endothelial nitric oxide synthase (eNOS, NOS-III, NOS-3 or Type III), mainly described in endothelial cells. ^[6]

Plasma nitrate concentrations were significantly higher in depressed patients, suggesting that the endogenous NO is involved in the pathogenesis of depression. NO activates soluble guanylyl cyclase, resulting in increase in cGMP levels. ^[7] cGMP would then activate cGMP-dependent kinase which further phosphorylates the 5-HT transporters and enhances the activity of 5-HT transporter. Thus cGMP mediated enhancement of the activity of 5-HT

transporter results in the reduction in the extracellular level of 5-HT. NO also modulates the release of 5-HT. NO negatively controls the extracellular levels of 5-HT in the hippocampus and the increased synthesis of NO result in suppression of 5-HT overflow. Inhibition of NO synthase enhances the activity of antidepressants that work via a serotonergic mechanism.^[8] Thus the increase in NO production following stressful situations can impair serotonergic transmission in the brain. NO also interact with selective 5-HT re-uptake inhibitors used in the treatment of depression.^[9] NO also modulates 5-HT_{1A} and or 5-HT_{1B} postsynaptic receptor function. Thus NO is involved in the pathogenesis of depression and the agents which suppress the NO production exerts antidepressants like effect.

TINOSPORA CORDIFOLIA

Tinospora cordifolia commonly named as "Guduchi" in Sanskrit belonging to family Menispermaceae is a genetically diverse, large, deciduous climbing shrub with greenish yellow typical flowers, found at higher altitude. In racemes or racemose panicles, the male flowers are clustered and female are solitary. The flowering season expands over summers and winters.^[10] Guduchi is also known as Giloe, Giloy, Gurchar (Hindi) and Amrta (Sanskrit). It is found almost everywhere in India and in Himalayas, even up to 1000 feet height. Its habitat ranges across a wide region in India spreading from Kumaon Mountains to Kanyakumari. It is also found in China, Myanmar, Sri Lanka, Thailand, Philippines, Indonesia, Malaysia, Borneo, Vietnam, Bangladesh, North Africa, West Africa and South Africa.^[11] A variety of active components derived from the plant like alkaloids, steroids, diterpenoid lactones, aliphatics, and glycosides have been isolated from the different parts of the plant body, including root, stem, and whole plant. *Tinospora cordifolia* contains alkaloids, glycosides, flavonoids, steroids and terpenoids in the aerial part of the plant.^[11] A variety of constituents used for drug preparation have been isolated from the plant. They belong to different classes such as alkaloids, diterpenoids lactones, glycosides, steroids, sesquiterpenoids, phenolics, aliphatic compounds, and polysaccharides. The alkaloids tinosporin, tinosporic acid, and tinosporol rich in protein,

calcium, and phosphorus have been identified in leaves.^[12] A large number of chemicals have been isolated from *Tinospora cordifolia*, belonging to different classes such as alkaloids, diterpenoid lactones, glycosides, steroids, sesquiterpenoid, phenolics, aliphatic compounds and polysaccharides. Leaves of this plant are rich in protein (11.2%), calcium and phosphorus.^[13] Four new clerodane furano diterpene glucosides (amritosides A, B, C and D) have been isolated as their acetates from stems. The structures of these compounds were established on the basis of spectroscopic studies.^[14]

TINOSPORA CORDIFOLIA AND DEPRESSION

Tinospora cordifolia extracts reduced the cytokine production, mitogenicity, stimulation and activation of immune effector cells.^[10] *Tinospora cordifolia* extract exerts strong free radical scavenging properties against superoxide anion (O₂⁻), hydroxyl radicals (OH), NO radical, and peroxynitrite anion (ONOO⁻).^[10] Petroleum ether extract of *Tinospora cordifolia* produce antidepressant-like effect by interaction with α_1 -adrenoceptors, dopamine D₂-receptors, serotonergic and GABA_B receptors, hence increasing the levels of norepinephrine, dopamine and serotonin; and decreasing the levels of GABA in brains of mice.^[15] *Tinospora cordifolia* extract also reduced the mouse whole brain MAO-A and MAO-B activities as compared to control.^[15] *Tinospora cordifolia* extract provides protection against oxidative stress, pro-inflammatory mediator release and redox signaling.

CONCLUSION

NO is involved in the pathogenesis of depression and the agents which suppress the NO production exerts antidepressants like effect. *Tinospora cordifolia* commonly named as Guduchi showed its strong free radical scavenging properties against superoxide anion (O₂⁻), hydroxyl radicals (OH), NO, and peroxynitrite anion (ONOO⁻). *Tinospora cordifolia* extract provides protection against oxidative stress, pro-inflammatory mediator release and redox signaling. Thus it has been concluded that the *Tinospora cordifolia* exerts beneficial effect in the depression through its NO scavenging activity.

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