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Integrated approach to combat depression with special reference to Medhya Rasayana

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Abstract
Depression is a significant contributor to the global burden of disease and affects people in all communities across the world. It is a state of low mood and aversion to any activity which affects a person's wellbeing. Ayurveda gives a prime role importance to mental health. According to latest health reports, Stress is said to be one of the largest killers of man today. It is now becoming more accepted as being crucially related to our total physical, mental, and spiritual health. Ayurveda describes it as a root cause of many diseases which disturbs the homeostasis of both the body and mind. There are a number of synthetic drugs which are being used as the standard treatment for clinically depressed patients and as also they have adverse effects which compromise the therapeutic treatment. Hence an attempt has made to review about the Medhya rasyana which demonstrate significant stress attenuating effects leading to depression in various experiments.

Keywords: Depression, Ayurveda, Medhya Rasayana

Introduction
Depression is a state of low mood and aversion to activity that can affect a person's thoughts, behavior, feelings and sense of well [1]. They may lose Interest in activities that once were pleasurable, experience loss of appetite or overeating, have problems concentrating, remembering details, or making decisions, and may contemplate or attempt suicide. Today, depression is estimated to affect 350 million people [2]. It is estimated that 1 million deaths per year occur due to causes of depression [3] in ayurvedic classical texts the description of the anxiety disorders is seen in the bhootvidya (psychiatric) segment. The basic definition of health in ayurveda is a state of physical and mental well-being. According to ayurveda, Satwa, Atma and Sharira are the three pillars of Life [4]. Health is a balanced state of Trigunas, Dhatus, Agni and mala. Vata, Pitta and Kapha determine the predominance of prakriti of a Person. Vishada and Avasada are two conditions which are closely similar to depression in Ayurveda. Charaka quotes 'Vishado Rogavardhananam Agrya:' [5] means Vishada is the foremost factor to worsen the disease condition. Medhya Rasayana drugs are used for prevention and treatment of mental disorders of all the age groups.
Ayurvedic approach of disease prevention involves therapeutic measures to delay ageing and rejuvenating whole functional dynamics of the body system. The concept of revitalization and rejuvenation approach in Ayurveda is known as the 'Rasayana chikitsa, one of the eight specialized branches of Ayurveda. It aims enhancement in strength, immunity, ojus, vitality, will power and determination of the body, longevity, memory, intelligence, excellence of luster, complexion and voice, optimum strength of physique and sense organs. Hence an integrated approach has made to discuss about the action of Medhya dravya's with respect to depression [6].

Depression
Most people feel depressed at times. Losing a loved one, getting fired from a job, going through a divorce, and other difficult situations can lead a person to feel sad, lonely, scared, nervous, or anxious. They may lose interest in activities that once were pleasurable, experience loss of appetite or overeating, have problems concentrating or making decisions, and may contemplate or attempt suicide. It is normal to feel sad on occasions. Sometimes this sadness will be from things which happen in our daily lives and we overcome it soon. But, there is a difference between 'normal' feeling and feelings caused by 'Clinical depression' in which normal experiences up's and down's whereas clinical depression experience specific symptom daily for two or three weeks making it different to function everywhere.

Pathology
In the manner of pathophysiology of depression, a neurochemical imbalance underlies the path physiology of mood disorders.

Neurochemical imbalances, namely in the synthesis and secretion of norepinephrine and serotonin, are thought to underlie depression. Since a whole spectrum of behaviours is disrupted during depressive episodes, it is unlikely that deregulation of a single neuro anatomical substrate can account for the disorder. Networking between different anatomical and neurochemical substrates in the onset of and recovery from depression.

Treatment for depression

Numerous antidepressants are discovered on the basis of their functional activity – the selective serotonin reuptake inhibitors (SSRIs) serotonin–norepinephrine reuptake inhibitors (SNRIs) including include buprenorphine, tryptophan, low-dose antipsychotics and other like norepinephrine reuptake inhibitors (NRIs), norepinephrine-dopamine reuptake inhibitors (NDRIs), norepinephrine-dopamine releasing agents (NDRAs), tricyclic antidepressants (TCAs), tetracyclic antidepressants (TeCAs), and monoamine oxidase inhibitors (MAOIs) [6, 7, 8, 9].

Ayurvedic concept of Depression

Emotions are the basic feelings of human beings. Our mind controls our Body. The mind is responsible for perception, thinking, understanding and taking the right decision at the right time [10]. Ayurveda is believed to cure human diseases through establishment of equilibrium in the different elements of human life, the body, the mind, the intellect and the soul [11]. The concept of interrelation of body, mind and soul is the building brick of modern psychology. Today there are many diseases that are related to mind i.e. default in one's perceptions, with body and conscious. Due to improper diet and disturbed state of mind i.e. positive feelings like love, affection and caring, helping nature are driven out. Hence our acharyas mention the causes of illness as

1) Lack of co-ordination between mental functions of Dhi [12], Dhriti [13] and Smriti [14]

2) Pragyaparadha [15].

The vitiation of manovaha srotas causes diseases like Unmada, Apasmara, Atattvaabhinivesha, Bhaya, Harsha, Shoka and depression also. In such condition person suffers from terrific dreams or it can manifest as psychosomatic disease [16]. The 'medhya rasayanas' are known to be beneficial to improve the intellectual property. Rasayana drugs acts as-

a) Immunomodulator: Increasing the ability of the immune system.

b) Adaptogen: Increases the ability of an organism to adapt to environmental factors e.g., Ashwagandha, Tulsi, haridra, Pippali, Amalaki, Guduchi, shatavari.

c) Antioxidant: Preventing the damage caused by oxygen free radical.

d) Nootropic: Promote intelligence and functions of brain e.g., Medhya Rasayana drugs (namely-Mandookparni, Guduchi, Yashtimadhu and Shankhpushpi).

How Medhya Rasayana is helpful in treating depression

Medhyarasayana drugs play an essential role in the treatment of psychiatric and psychosomatic diseases. The mode of this therapy involves the individual to attain sedation, calmness, tranquility or a stimulation of activities of brain [17]. Based on the experimental and clinical research, it is known that these drugs have varying degree of psychotropic action and are known to possess antidepressant, sedative and tranquilizing action. Medhya Rasayana drugs are used for prevention and treatment of mental disorders of all the age groups. These drugs promote the Intellect (Dhi) Retention power (Dhriti), memory (Smriti). Medhya Rasayana drugs are known to have specific effect on mental performance by promoting the functions of "Buddhi" and "Manas" by correcting the disturbances of "Rajas" and "Tamas" [18].

Table 1

Medhya dravya	Synonyms	Properties			
		Rasa	Guna	Vipaka	virya
1. Yastimadhu (Glycyrrhiza glabra Linn., Family – Fabaceae	Yasti, madhuka, Klitaka. Dosha karma – Vata- pitta shamak	Madhura	*Guru, Snigdha*	*Shita*	*Madhura*
2. Guduchi (*Tinospora cordifolia* Willd. Miers, Family – Menispermaceae)	Amrita, Madhuparni, Chinnamula, Cakra-lakshanika, Amrita-valli, Chinna, Chin-nodhbhava, Vatsadani, Jivanti, Tantrika, Soma, Somavalli, Kundali, Dheera, Vi-shalya, Rasayani, Candrahasa, Vayastha, Mandali, Deva-nirmita. Dosha karma – Tri-dosha shamak	Tikta, Kasaya	*Guru, Snigdha*	*Usna*	Madhura
3. Shankhapushpi (*Convolvulus pleuricaulis* Chois. Family – Convolvula-ceae)	Ksheerpushpi, Mangalyakusuma. Dosha karma – Vata-pitta shamak	Tikta	*Snigdha, Picchila*	Shita	*Madhura*
4. Brahmi (Bacopa monniera *Linn. Family – Scrophulariaceae*)	Swarya, smritiprada Dosha karma-kapha pitta hara, medya, aayushya, rasayani.	Tikta	Laghu	Ushna	Katu

Work on Medhya Rasayana

1) Yashtimadhu *(Glycyrrhiza glabra)*

Dinesh Dhingra *et al*., (2005) Glycyrrhizin (1.5, 3.0 and 6.0 mg/kg, i.p.) was administered once daily for seven successive days to separate groups of young male Swiss albino mice. The immobility periods of control and treated mice were recorded in forced swim test (FST) and tail suspension test (TST). Effect of sulpiride (50 mg/kg, i.p.; a selective D2 receptor antagonist), prazosin (62.5 µg/kg, i.p.; an a1-adrenoceptor antagonist) and p-chlorophenylalanine (100 mg/kg, i.p.; an inhibitor of serotonin synthesis) on antidepressant-like effect of glycyrrhizin in TST was also studied. The antidepressant-like effect of glycyrrhizin was compared to that of imipramine (15 mg/kg, i.p.) and fluoxetine (20 mg/kg, i.p.) administered for seven successive days. Glycyrrhizin, a triterpene saponin, possess anti-inflammatory [19], antithrombotic [20], antiviral [21], and antiulcer [22], activities. Glycyrrhizic acid administered in drinking water at a concentration of 1 mg/ml for 10 days partially blocked the stress response and increased adaptation in rats [23]. Glycyrrhizic acid competitively inhibits 11 beta-hydroxysteroid dehydrogenase type-2 (11 beta-HSD2) enzymatic activity [24]. Glycyrrhizic acid is hydrolysed in the intestine to the pharmacologically active compound glycyrrhetic acid, which inhibits the enzyme 11 beta-

hydroxysteroid dehydrogenase (in the direction of cortisol to cortisone) as well as some other enzymes involved in the metabolism of corticosteroids. Inhibition of 11 beta-hydroxysteroid dehydrogenase leads to increased cortisol levels in the kidneys and in other mineralocorticoid-selective tissues. Since cortisol, which occurs in much larger amounts than aldosterone, binds with the same affinity as aldosterone to the mineralocorticoid receptor, the result is a hypermineralocorticoid effect of cortisol leading to sodium retention, potassium loss and suppression of the rennin-angiotensin-aldosterone system, thus leading to adverse effects such as hypertension and oedema. There is apparently a great individual variation in the susceptibility to glycyrrhizic acid. A daily intake of 10 mg glycyrrhizic acid would represent a safe dose for most healthy adult human beings. Increased motor activity was not involved in the action seen in both FST and TST, and confirms the assumption that the antidepressant-like effect of glycyrrhizin is specific. Glycyrrhizin might produce antidepressant-like effect by interaction with a_1-adrenoceptors and dopamine D_2-receptors, thereby increasing the levels of norepinephrine and dopamine in brains of mice. Since glycyrrhizin has MAO inhibiting activity [25], therefore, antidepressant-like effect of glycyrrhizin in mice might be through increase in the brain levels of monoamines like epinephrine and dopamine by inhibiting monoamine oxidase.

2) Guduchi *(Tinospora cordifolia)*

Dr Madhav Mutalik (2011) [28], *Tinospora cordifolia* is claimed to be useful in maintaining healthy brain function and in stress management (Mentalife 2011). The extracts have been shown to have antidepressant effects on learned helplessness in mice and rat models of depression (Dhingra 2006). The neuroprotective activity of ethanol extract of *Tinospora cordifolia* aerial parts have been shown in a study involving 6-hydroxy dopamine (6-OHDA) lesion rat model of Parkinson's disease (PD) [26]. The antidepressant activity of *Tinospora cordifolia* was shown in Swiss albino mice by the tail suppression test and forced swim test on oral administration of its petroleum ether extract in the doses of 50, 100 and 200mg/kg. The efficacy of its antidepressant activity was comparable to 15 mg/kg of imipramine (a TCA) and 20 mg/kg of sertraline (an SSRI). Thus the mechanism of the antistress and antidepressant activities of *Tinospora cordifolia* most likely relates to increased levels of norepinephrine, dopamine and serotonin, and decreased level of gammaaminobutyric acid (GABA), resulting from interaction with alpha-1 adrenergic, dopaminergic (D2), serotonergic and GABA-B receptors (Dhingra 2006, Dhingra 2008) [6]. The supportive evidence is in terms of normalisation of stress induced biochemical changes in norepinephrine, dopamine and 5-hydroxytryptamine in experimental rat models and improved levels of 5-hydroxyindoleacetic acid (5-HIAA) (a metabolite of 5-HT) in mice with ethanolic roots extracts (Singh J 2003). Modern antidepressants act by inhibiting reuptake or breakdown of one or more of these amines and increasing their levels at postsynaptic receptors. Tricyclic antidepressants (TCAs) (e.g. imipramine, amitriptyline) nonspecifically inhibit the reuptake of brain amines.

3) Shankhapushpi *(Centella asciatica)*

Dhingra (2007), the effect of petroleum ether, chloroform and ethyl acetate fractions of total ethanolic extract of *Convolvulus pluricaulis* Choisy (Family-Convolvulaceae) on depression in mice. Petroleum ether fraction (25 and 50 mg/kg), chloroform fraction (25, 50 and 100 mg/kg) and ethyl acetate fraction (25, 50 and 100 mg/kg) were administered orally for 10 successive days in separate groups of Swiss young male albino mice.

The effects of extracts on immobility periods of mice were assessed in forced swim test (FST) and tail suspension test (TST). The antidepressant-like effect of the extracts was compared to that of imipramine (15 mg/kg p.o.) and fluoxetine (20 mg/kg p.o.) administered for 10 successive days. The result showed that only chloroform fraction (50 and 100 mg/kg) of total ethanolic extract produced significant antidepressant-like effect in mice in both TST and FST and its efficacy was found to be comparable to fluoxetine and imipramine. Therefore, this suggests that antidepressant-like effect of chloroform fraction might be through the restoration of brain monoamines, like norepinephrine, 5-hydroxytryptamine and dopamine levels. *Convolvulus pluricaulis* showed reduction in the level of plasma cortisol, Thus it might be possible that antidepressant like effect of chloroform fraction might be due to reduction in plasma cortisol levels.

4) Brahmi *(Bacopa monniera Linn.)*

SLDV Ramana Murty Kadali *et al*., (2014) study was conducted to assess the antidepressant activity of brahmi in albino mice in forced swimming test, tail suspension test 36 and shock induced depression were used for this study. TST, FST and shock induced models of depression which provides a rapid and reliable behavior screening test for antidepressants. In FST tese Fluoxetine did not show any significant effect [28, 29]. Imipramine (10mg/kg), brahmi (10, 20,30mg/kg) significantly decreases the duration of immobility by 36.87%, 56.33%, 56.96% and 69.86% respectively. In TST Imipramine (10mg/kg), fluoxetine (30mg/kg) significantly decreases the duration of immobility by 47.67%, 37.43% respectively. But brahmi did not produce any effect in the doses studied (10, 20 & 30 mg/kg). However Manavi Chatterjee *et al*., [29] used higher doses like 40,80,160 mg/kg has shown significant effect in TST model. Shock has significantly decreased the activity in photoactometer, suggesting shock has produced depression. Imipramine (10mg/ kg), fluoxetine (30mg/kg), brahmi (10,20,30mg/kg) had significantly retain the activity by 77%, 99.5%, 93.4%, 95%, 133.3% respectively indicates the antidepressant activity in shock induced depression. Three different doses of brahmi exhibited antidepressant activity in mice in FST and SID models. It failed to demonstrate antidepressant activity in the TST model.

Discussion

The current generation is facing depression and anxiety disorders partly due to elevated work related stress, detachment from the community, addictions, etc. According to modern science, depletion of certain neuro transmitters like Serotonin and or epinephrine at the synapses forms the neurochemical basis for depression. Ancient Ayurvedic approach of disease prevention involves therapeutic measures to delay ageing and rejuvenating whole functional dynamics of the body system. The fact that ‘prevention is better than cure’ is well recognized in Ayurveda, as its foremost objective is maintenance and promotion of the health of the healthy. Neurological and psychiatric disorders are generally associated with loss of memory, cognitive deficits, impaired mental function etc. The 'medhya rasayanas' are known to be beneficial to improve the intellectual The word 'medhya rasayanas', have been derived from the Sanskrit words

'medhya', meaning intellect or cognition, and 'rasayana', meaning 'rejuvenation. Medhya rasayana drugs play an essential role in the treatment of psychiatric and psychosomatic diseases.

Conclusion

The diseases in which depression is implicated in the aetiopathogenesis, has a logical place for rasayana in their management. However, appropriate scientific evidence needs to be generated for their widespread acceptance. This, in turn, necessitates concerted efforts to investigate the effects of possible pharmacodynamic and pharmacokinetic actions of Medhya Rasayana. Thus plant based formulation are useful in mild to moderate cases of depression.

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