

Antidepressants: Mechanism of Action, Toxicity and Possible Amelioration

Abstract

Depression being a state of sadness may be defined as a psychoneurotic disorder characterised by mental and functional activity, sadness, reduction in activity, difficulty in thinking, loss of concentration, perturbations in appetite, sleeping, and feelings of dejection, hopelessness and generation of suicidal tendencies. It is a common and recurrent disorder causing significant morbidity and mortality worldwide. The antidepressant compounds used against depression are reported to be used also for treating pain, anxiety syndromes etc. They have been grouped in five different categories such as

- I. Tricyclic antidepressants (TCAs)
- II. Selective serotonin-reuptake inhibitors (SSRIs)
- III. Monoamine oxidase inhibitors (MAOIs)
- IV. Serotonin-norepinephrine reuptake inhibitor (SNRI) and
- V. Non-TCA antidepressants based on their mode of action.

Most of the antidepressants have been reported to possess adverse effects on the health of users. The present review article focuses on an updated current of antidepressants, their mechanism of actions, pathophysiology of these compounds, their side effects and the strategies to combat the drug induced toxicity. An account of phytochemicals found to be acting as antidepressant is also included.

Keywords: Depression; Antidepressants; Toxicity; Neurotransmitters; Biomarkers

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Abbreviations: TCAs: Tricyclic Antidepressants; SSRIs: Selective Serotonin-Reuptake Inhibitors; MAOIs: Monoamine Oxidase Inhibitors; SNRI: Serotonin-Norepinephrine Reuptake Inhibitor; PMDD: Premenstrual Dysphoric Disorder; SAD: Seasonal Affective Disorder; PMS: Premenstrual Syndrome; NE: Norepinephrine; 5-HT: 5-Hydroxytryptamine; DA: Dopamine; CNS: Central Nervous System; NRI: Noradrenalin Specific Reuptake Inhibitor

Introduction

Depression may be defined in terms of a state of feeling sad. It may also be defined as a psychoneurotic disorder characterised by mental and functional activity, sadness, reduction in activity, difficulty in thinking, loss of concentration, perturbations in appetite, sleeping, and feelings of dejection, hopelessness and generation of suicidal tendencies [1]. It is a common and recurrent disorder causing significant morbidity and mortality worldwide [2,3]. Depression, a kind of mental illness, includes arousal of grief which may affect the overall thinking process, behaviour and feelings [1]. Such persons suffer from an imbalanced sleep and sleeping disorders [4-6]. Several workers [7,8] have described the causes of depression which include genetic, heterogeneous parental behaviour to the siblings, neglect and sexual abuse. In addition, certain conditions like difficulties in job, relationships,

natural disasters, finances, child birth, catastrophic injury, loss of life of loved ones and menopause [9,10]. It is known that different brain regions may mediate the onset of variety of symptoms of depression as they regulate emotions, neural circuitry and mood. There is meagre information available about the underlying mechanisms of their regulations. The malfunctioning of the hypothalamus region of the brain has been found to be associated with very less or too much sleep, disinterest in sex and other activities of enjoyment. Depression in general has three main forms such as

- I. Psychotic depression characterised by severe depression,
- II. Postpartum depression characterised by perturbations in the levels of hormones and physical features after child birth and
- III. Seasonal Affective Disorder (SAD) concerning specially the winter months with less sunlight [11].

In the women, the depression arises also due to extra work load, domestic responsibilities, child care, strained relationship, care of aged parents and poverty. In addition to all these indices, the psychological, biological and hormonal factors also significantly contribute in depression. The premenstrual dysphoric disorder (PMDD) or premenstrual syndrome (PMS) and osteoporosis in women can play important role in development of depression.

Depression in men may be associated with sufferings from serious diseases such as cancer and cardiac diseases, extreme tiredness, irritation, disinterest in once-pleasurable activities, loss of balance, less sleep and getting aggressive. In older men, arteriosclerotic depression (vascular depression) has been observed. The depression which may lead to suicide in the children may be associated to the emerging sexuality and onset of puberty. The present article is an endeavour to illustrate an updated account and varied aspects of depression such as its pathophysiology, symptoms, diagnosis, treatment with drugs and their mode of actions, toxicity and use of plant products as potential antidepressants.

Pathophysiology of depression

There are no useful biomarkers or imaging abnormalities to determine pathophysiology of depression during life time. The post-mortem study of brain does not reveal any consistent structural or neurochemical abnormality. Majority of the currently available medications were discovered empirically. Most current theories are based on "amine hypothesis" [12]. The most important hypothesis of mood disorder is related to the alterations in the levels of biogenic amines [13-15]. It states that depression is caused by a functional deficiency of catecholamines, particularly norepinephrine (NE), whereas mania is caused by a functional excess of catecholamines at the critical synapses in the brain. The occurrence of depression has been found to be associated with the alterations in the levels of biogenic amines in the brain such as NE, dopamine (DA) and epinephrine, indolamine, serotonin, 5-hydroxytryptamine (5-HT) and two catecholamines.

Antidepressants

Antidepressants are those drugs which help in the reduction in symptoms of depressive disorders by altering chemical imbalances of neurotransmitters in the brain. The change in mood and behaviour is due to chemical imbalance. Neurotransmitters are the communication link between neurons in the brain. Neurotransmitters are located in vesicles found in nerve cells. The neurotransmitters such as serotonin, dopamine and noradrenaline or norepinephrine are released by the axonic end of one nerve and received by the other; the phenomenon called as reuptake. The antidepressants inhibit reuptake of neurotransmitters through selective receptors thereby increasing the concentration of specific neurotransmitter around the nerves in the brain. One of such antidepressant is selective serotonin reuptake inhibitor (SSRI), which affects the brain serotonin level. Antidepressants may recover the signs of depression, but also exert some side-effects. They are used in the medication of a number of symptoms, including not only depression, some anxiety disorder, nervousness, OCD, manic-depressive disorders, bedwetting in childhood, major depressive disorder, diabetic peripheral neuropathic pain, social fretfulness, post-traumatic stress disorder etc. and some conclude, but not perfect in fibromyalgia, chronic hives (allergic reaction), flashes, drug induced hyperhidrosis (sweating in excess), premenstrual symptoms, pruritus (itching), nervosa, tourette, binge eating disorder etc. The medicines achieve their desired function by

adversely influencing the concentrations of neurotransmitters in the brain such as NE, serotonin and dopamine and the central nervous system (CNS). Based on the mode of actions, a group of antidepressants contain 17 substances which can be further divided into subgroups. The commonly used medicines against depression are summarised in Table 1.

Antidepressants and their classification

Imipramine was discovered in 1958 as an antidepressant regimen [17]. The antidepressants have been divided into five groups:

- i. Tricyclic antidepressants (TCAs),
- ii. Selective serotonin-reuptake inhibitors (SSRIs),
- iii. Monoamine oxidase inhibitors (MAOIs),
- iv. Serotonin-norepinephrine reuptake inhibitor (SNRI) and
- v. Non-TCA antidepressants.

The TCAs block the reuptake of both norepinephrine (NE) and serotonin (5HT). This phenomenon being the primary mechanism of actions of antidepressants brings changes in the physiological behaviour of neuro-receptors. TCAs have also been reported to block muscarinic, alpha1 adrenergic and histaminic receptors. However, these molecules may lead to occurrence of different side effects in patients as summarised in Table 2.

Mourilhe [20] have reported that the Selective serotonin-reuptake inhibitors (SSRIs) may block the reuptake of 5HT and increase synaptic 5HT transmission. The SSRIs have very little or insignificant effect on the reuptake of other neurotransmitters. It has been observed that SSRIs does not display any activity at the muscarinic and histaminergic receptors which probably results into minute anti-cholinergic (ACH) and sedative effects (Table 3).

The mechanisms of actions of different antidepressants such as monoamine oxidase inhibitors (MAOIs), phenelzine (Nardil) and tranylcypromine (Parnate) associate with the inhibition of the enzymatic conversion of 5HT and NE into their corresponding metabolites. MAOIs are generally prescribed in cases of atypical or drug resistant depression. These compounds contain a certain level of toxicity. On the contrary to it, the moclobemide (manerix) has been reported to be the first reversible inhibitor of monoamine oxidase A (RIMA). This molecule is found relatively more effective and safe [23]. Another antidepressant, nefazodone (serzone) has properties of both: it acts like SSRIs which blocks the reuptake of 5HT and also act as an antagonist of 5HT₂ receptor [23] thereby reducing the stimulating effects similar to SSRIs. Nefazodone has structural and pharmacological similarities to another antidepressant, trazodone (desyrel). The only difference is that nefazodone binds with α_1 receptors with low affinity. All of these antidepressants do not significantly influence ACH mediated functions (Table 4).

The activity of serotonin nor-epinephrine reuptake inhibitors (SNRIs) does not exert any side effects such as sedation or hypotension but display TCAs like activity [23]. Higher doses

of SNRIs have been reported to mildly increase blood pressure. The above mentioned antidepressants in adequate dosages exhibit same level of effects for treatment of depression. Some of the SNRIs are duloxetine (Cymbalta), venlafaxine (Effexor XR), desvenlafaxine (Pristiq, Khedezla) and levomilnacipran (Fetzima). The first line of antidepressants is the Non-TCAs (NTCA) which includes SSRIs. These agents are relative safer with better

tolerability. Those patients which do not show any response to other drugs or suffering from chronic pain or migraine are given TCAs. However, the existing reports suggest that the secondary amine TCAs (desipramine and nortriptyline) possess more side effects than tertiary amine TCAs (Table 5). A comparative estimate of antidepressants and their therapeutic properties are summarised in Table 6.

Table 1: Commonly used antidepressants and their mechanisms of actions [16].

c	ATC-Code	Name of Substance	Pharmaceutical Name	Mechanism of Action
1	N06AA04	Clomipramine	Anafranil- Novartis + generics	Serotonin-norepinephrine reuptake inhibitors
2	N06AA06	Trimipramine	Surmontil- sanofiaventis	Serotonin-norepinephrine reuptake inhibitors
3	N06AA09	Amitriptyline	Saroten- lundbecktryptizol- msd	Serotonin-norepinephrine reuptake inhibitors
4	N06AA10	Nortriptyline	Sensaval- lundbeck	Serotonin-norepinephrine reuptake inhibitors
5	N06AA21	Maprotiline	Ludiomil- Novartis + generics	Serotonin-norepinephrine reuptake inhibitors
6	N06AB03	Fluoxetine	Fontex- lilly + generics	Serotonin Reuptake inhibitors
7	N06AB04	Citalopram	Cipramil- lundbeck + generics	Serotonin Reuptake inhibitors
8	N06AB05	Paroxetine	Seroxat- glaxosk + generics	Serotonin Reuptake inhibitors
9	N06AB06	Sertraline	Zoloft-Pfizer + generics	Serotonin Reuptake inhibitors
10	N06AB08	Fluvoxamine	Fevarin- solvaypharma	Serotonin Reuptake inhibitors
11	N06AB10	Escitalopram	Ciprallex- lundbeck	Serotonin Reuptake inhibitors
12	N06AG02	Moclobemide	Aurorix- roche + generics	MAO inhibitor

Table 2: Antidepressants and their side effects.

Sr. No.	Antidepressant Substrate (Common Name)	Doses	Therapeutic Index (TI)	Side-Effects	Toxicity in overdose	References
1	Amitriptyline	start with a dosage of up to 100 mg/day	Narrow	Confusion, Numbness and Tingling In Your Arms and Legs, Headache, Constipation Or Diarrhoea, Blurred Vision, Skin Rash, Swelling Of Your Face and Tongue, Nausea, Unexpected Weight Gain Or Loss	High	[18]
2	Amoxapine	50 mg-100 mg maximum dose: 600 mg/day	Narrow	Dizziness or light headedness, confusion, constipation, difficulty in urinating, dry mouth	-	
3	Clomipramine	25 mg, 100 mg, 250 mg/day	Narrow	Dizziness or light headedness, confusion, constipation, difficulty in urinating, dry mouth	Moderate	
4	Desipramine	100-300 mg/day	Narrow	Dizziness or light headedness, confusion, constipation, difficulty in urinating, dry mouth	-	
4	Doxepin	25-300 mg/day	Narrow	Dizziness or light headedness, confusion, constipation, difficulty in urinating, dry mouth	-	
5	Imipramine Hydrochloride	10-50 mg/day	Narrow	Dizziness or light headedness, confusion, constipation, difficulty in urinating, dry mouth	High	

6	Imipramine Pamoate	10-50 mg/day	Narrow	Dizziness or light headedness, confusion, constipation, difficulty in urinating, dry mouth	High	
7	Maprotiline	-	Narrow	Dizziness or light headedness, confusion, constipation, difficulty in urinating, dry mouth	-	
8	Nortriptyline	10-25 mg/day	Narrow	Dizziness or light headedness, confusion, constipation, difficulty in urinating, dry mouth	High	
9	Protriptyline	-	Narrow	Dizziness or light headedness, confusion, constipation, difficulty in urinating, dry mouth	-	
10	Trimipramine	-	Narrow	Dizziness or light headedness, confusion, constipation, difficulty in urinating, dry mouth	High	[19]

Table 3: Side effects of use of SSRIs.

Sr. No.	Antidepressant Substrate (Common Name)	Doses	Therapeutic Index	Side-Effects	Toxicity due to Overdose	References
1	Citalopram	20-40 mg/day	Wide	Nausea, Anxiety, Insomnia Dry Mouth, Headache, Somnolence, Dizziness, Agitation, Anorexia, Diarrhoea, Constipation, Tremor, Sweating, Sexual Dysfunction	Moderate	[21]
2	Fluoxetine	10-20 mg and 4mg/day	Wide	Nausea, Anxiety, Insomnia Dry Mouth, Headache, Somnolence, Dizziness, Agitation, Anorexia, Diarrhoea, Constipation, Tremor, Sweating, Sexual Dysfunction	Low	[22]
3	Fluvoxamine	50-100 mg/day	Wide	Nausea, Anxiety, Insomnia Dry Mouth, Headache, Somnolence, Dizziness, Agitation, Anorexia, Diarrhoea, Constipation, Tremor, Sweating, Sexual Dysfunction	Low	[22]
4	Paroxetine	20-30 mg/day	Wide	Nausea, Anxiety, Insomnia, Dry Mouth, Headache, Somnolence, Dizziness, Agitation, Anorexia, Diarrhoea, Constipation, Tremor, Sweating, Sexual Dysfunction	Low	[22]
5	Sertraline	25-100 mg/day	Wide	Nausea, Anxiety, Insomnia Dry Mouth, Headache, Somnolence, Dizziness, Agitation, Anorexia, Diarrhoea, Constipation, Tremor, Sweating, Sexual Dysfunction	Low	[22]
6	Nefazodone	100-200mg/day	Wide	Nausea, Anxiety, Insomnia Dry Mouth, Headache, Somnolence Dizziness Agitation Anorexia, Diarrhoea, Constipation, Tremor, Sweating, Sexual Dysfunction	-	[22]
7	Trazodone	50-100 mg/day	Wide	Nausea, Anxiety, Insomnia Dry Mouth, Headache, Somnolence Dizziness Agitation Anorexia, Diarrhoea, Constipation, Tremor, Sweating, Sexual Dysfunction	-	[22]

Interaction of antidepressants with the cellular receptors

As explained above, the MAOIs block the metabolism of neurotransmitters such as NE, DA and 5-HT and cause increase in the concentration of monoamine transmitters. The traditional MAOIs (tranylcypromine) act in irreversible and non-selective manner whereas the recently investigated MAOIs are reversible

in binding and very selective for MAO-A or MAO-B. TCAs is a combo drug [30] containing at least five chemical agents with different activities such as a serotonin reuptake inhibitor activity, a norepinephrine reuptake inhibitor activity, an anti-cholinergic anti-muscarinic activity, an alpha-1-adrenergic antagonist activity, and an antihistamine (H1) activity [31]. When taken in overdose, they cause toxicity in terms of lethal cardiac arrhythmias and seizures. The mechanism of action of TCAs relies on the

inhibition of reuptake of serotonin and NE [31]. The different members of TCAs display differential inhibition activity on 5HT and NE transporters. Clomipramine has been reported to be the most potent at 5-HT reuptake pump whereas desipramine and

maprotiline were more potent at NE reuptake pump. The drug toxicity of TCAs has been explained in terms of their effects on certain receptors such as H1, M1, and α 1.

Table 4: Doses and side effects of some other antidepressants.

Sr. No.	Antidepressant Substrate (Common Name)	Doses	Therapeutic Index	Side-Effects	Toxicity in Overdose	References
1	Isocarboxazid	40-60 mg/day	Wide	Dizziness, Headache, Tremors Or Shaking; Constipation, Nausea; Or Dry Mouth.	High	[24]
2	Phenelzine	60 mg/day	Wide	Dizziness, Headache, Drowsiness, Sleep Disturbances (Including Insomnia, Hypersomnia), Fatigue, Weakness, Tremors, Twitching, Myoclonic Movements, Hyperreflexia	High	[25]
3	Tranlycypromine	60 mg/day	Wide	Scleroderma, Flare-Up Of Cystic Acne, Ataxia, Confusion, Disorientation, Memory Loss, Urinary Frequency, Urinary Incontinence, Urticaria, Fissuring In Corner Of Mouth, Akinesia	Low	[26]
4	Moclobemide	300 mg/day	Wide	Nausea, Dry Mouth, Constipation, Diarrhoea, Anxiety, Restlessness, Insomnia, Dizziness	High	[27]

Table 5: Doses and adverse effects of application of Non-TCA (NTCA) antidepressants.

Sr. No.	Antidepressant Substrate (Common Name)	Doses	Therapeutic Index	Side-Effects	Toxicity in Overdose	References
1	Agomelatine	25-50 mg/day	Narrow	Dizziness Abnormal Changes In Liver Function Tests Abdominal Pain	Unclear	[22]
2	Bupropion	150 mg/day	Narrow	Insomnia, Nausea, Pharyngitis, Weight Loss, Constipation, Dizziness, Headache, And Xerostomia	Moderate	
3	Duloxetine	60 mg/day	Wide	Asthenia, Constipation, Diarrhea, Dizziness, Drowsiness, Fatigue, Hypersomnia, Insomnia, Nausea, Sedation, Headache, and Xerostomia.	Moderate	
4	Mianserin	30-200 mg/day	Narrow	Drowsiness, Liver Dysfunction, Jaundice, Gynaecomastia, Convulsions, Hypomania, Hypotension, Hypertension; Coma, Arthralgia, Oedema, Tachycardia, Bradycardia, Vomiting, Dizziness and Ataxia, Anti-cholinergic Effects	Low	
5	Reboxetine	8mg/Day	Narrow	Urinating problem, Dry Mouth, Sweating, Tingling or Numbness of The Hands or Feet, Constipation, Increase in Blood Pressure, Increase in Heart Rate, Impotence, Insomnia, Headache, Dizziness, Nausea, Decreased Appetite	Low	
6	Trazodone	150-400 mg/day	Wide	Blurred vision, Dizziness, Drowsiness, Headache, Nausea, Vomiting, and Xerostomia Syncope, Edema, Ataxia, Confusion, Diarrhea, Hypotension, Insomnia, Sedation, and Tachycardia	Low	

7	Venlafaxine	75 mg/day with Food (37.5 mg/day if Anxious or Debilitated)	Narrow	Bipolar Disorder (Manic Depression); Cirrhosis Or Other Liver Disease, Kidney Disease, Heart Disease, High Blood Pressure, High Cholesterol, Diabetes; Narrow-Angle Glaucoma, A Thyroid Disorder, A History of Seizures, A Bleeding or Blood Clotting Disorder, Low Levels of Sodium in Your Blood	Moderate
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Table 6: A comparative estimate of antidepressants and their therapeutic properties [28,29].

Sr. No.	Type of Anti-depressants	Name of Anti-depressant	Half-Life	Availability	Dietary Consideration	Reference
1	SSRIs	Citalopram	About 36 hours	Tablet	Contains Lactose	[28]
		Escitalopram	About 30 hours	Tablets	-	
		Fluoxetine	96-144 hours (4-6 Days)	Dispersible Tablets*/ Capsules	Contains Gelatin	
		Fluvoxamine	17-22 Hours	Tablet	-	
		Paroxetine	About 24 Hours	Tablet	-	
		Sertraline	22-36 Hours	Tablet	-	
2	SNRIs	Duloxetine	8-17 Hours	Capsules	Contains Gelatin	
		Venlafaxine	4-7 Hours	Capsules	Contains Gelatin	
3	Tricyclics	Amitriptyline	9-25 Hours	Tablets	-	
		Dosulepin	About 50 Hours (Just Over 2 Days)	36 Hours	-	
		Clomipramine	36 Hours	Tablets	-	
		Doxepin	33-80 Hours (1.5-3.3 Days)	Capsules	Contains Lactose	
		Imipramine	About 19 Hours	Liquid	Contains Lactose	
		Lofepramine	12-24 Hours	Tablets	Contains Lactose	
		Nortriptyline	About 36 Hours	Tablets	Contains Lactose	
		Trimipramine	About 23 Hours	Capsules	Contains Lactose	
4	Tricyclic-Related Drugs	Mianserin	6-39 Hours	Tablets	Contains Lactose	
		Trazodone	5-13 Hours	Tablets	Contains Lactose	

5	MAOIs	Isocarboxazid	About 36 Hours	Tablets	Contains Lactose
		Phenelzine	11-12 Hours	Tablets	Requires Food Restrictions
		Moclobemide	2-4 Hours	Tablets	Requires Food Restrictions
		Tranlycypromine	About 2 Hours	Tablets	Requires Food Restrictions
6	Others	Agomelatine	1-2 Hours	Tablets	Contains Lactose
		Mirtazapine	20-40 Hours	Liquid	-
		Reboxetine	About 13 Hours	Tablets	-
		Triptafen	N/A	Tablets	-
		Vortioxetine	About 66 Hours	Tablets	-

*Dispersible tablets will disintegrate quickly in the mouth or can be mixed with water, orange juice or apple juice.

*All other antidepressants currently available do not contain lactose or gelatin, and do not require any specific dietary restrictions, although caution when drinking alcohol is a recommended for all antidepressants.

Selective serotonin reuptake inhibitors (SSRIs)

SSRIs are known to selectively inhibit serotonin transport. Some of the SSRIs are fluoxetine (Prozac, Selfemra), paroxetine (Paxil, Pexeva), sertraline (Zoloft), citalopram (Celexa) and escitalopram (Lexapro). This action of SSRIs results into abrupt increase in serotonin in the somatodendritic area of serotonergic neurons which causes desensitization of the somatodendritic serotonin-1A autoreceptors [31-33]. As a result, the neuronal impulse flow is increased [33]. It causes increased release of serotonin from axon terminals, which culminates into desensitization of postsynaptic serotonin receptors. Desensitization of these receptors may contribute to the therapeutic actions of SSRIs or it could account for the development of tolerance to acute side effects of SSRIs. The pharmacological analysis of SSRIs suggests that these agents may cause strong but slow disinhibition of 5-HT neurotransmission in the central nervous system (CNS). In this case, the actions of antidepressants are mediated by a pathway from midbrain raphe to prefrontal cortex [34,35]. The side effects generated by SSRIs include anxiety, sleep disturbances, sexual dysfunction (decreased libido, reduced pleasurability and reduction in arousal), and gastrointestinal disturbances [30]. It is thought that the toxicity the 5-HT2 and 5-HT3 receptors of certain serotonergic pathways are responsible. A reciprocal relationship exists between serotonin and dopamine viz. serotonin tending to inhibit sexual functioning and dopamine tending to enhance sexual functioning. It is believed that serotonin pathway descending from brain stem down the spinal cord to spinal neurons that mediate various spinal reflexes is responsible for the sexual dysfunction in the form of ejaculation and orgasm problems. It has been reported that the enhanced serotonergic flow through this pathway inhibits sexual

functioning. The serotonin's negative effects on sexual functioning are mediated via 5-HT2 receptors. Therefore 5-HT2 antagonists can reverse SSRIs induced sexual dysfunction [36,37].

The antidepressant acting as serotonin/norepinephrine/dopamine reuptake inhibitor (SNRI)

Stahl [30] have demonstrated the pharmacologic effect of venlafaxine and found it to be dose dependent. At low doses, it essentially acts as an SSRI and at medium to high doses, it causes additional NE reuptake inhibition and at very high doses, DA reuptake inhibition occurs [30,39]. Other antidepressants such as nefazodone and trazodone act via serotonin-2 receptor antagonism with serotonin reuptake blockade. It is interesting to mention here that SSRIs stimulate 5-HT2 receptors where as nefazodone and trazodone blocks the receptor [30]. This action of nefazodone and trazodone makes it safer antidepressants than the SSRIs.

Depressants as norepinephrine and dopamine reuptake inhibitor (Bupropion)

Bupropion is the only antidepressant that selectively acts on the noradrenergic and dopaminergic systems and not on the serotonin system [40]. Bupropion exhibits dopaminergic and noradrenergic activity, therefore it may exert positive effect in overcoming the attention deficit disorder [41] and in the treatment of smoking cessation [38]. In contrary to the benefits from this drug, bupropion has been shown to induce some side effects such as overstimulation, agitation, insomnia and nausea [30,39].

Antidepressants showing α -2 antagonism plus serotonin-2 and serotonin-3 antagonism

Mirtazapin, a noradrenergic and specific serotonergic antidepressant [43], has both pro-adrenergic and proserotonergic actions. The pro-adrenergic and proserotonergic actions of mirtazapin are due to its α 2-antagonist properties i.e. disinhibition of both serotonin and norepinephrine neurotransmission. Similar to nefazodone, mirtazapin also does not exert any toxicity of SSRIs due to 5-HT₂ stimulation. Since strong antihistamine properties are associated to mirtazapin, it has some side effects such as weight gain and sedation [30,39].

The antidepressants acting as a noradrenalin specific reuptake inhibitor (NRI) (Reboxetine)

Reboxetine, a noradrenaline (norepinephrine) reuptake inhibitor, is exclusively unrelated to TCA or SSRIs. The specific properties of reboxetine includes its high affinity for the noradrenaline transporter, and little affinity for other neuro receptors including serotonin, dopamine, histamine, muscarinergic and alpha adrenergic sites [43].

Antidepressants as a serotonin reuptake enhancer (Tianeptine)

Tianeptine being, a tricyclic compound of dibenzothiazepine type increases the presynaptic uptake of serotonin after single as well as repeated administration, but this action is not linked to any effects on the 5-HT post-synaptic systems [50,89]. Tianeptine has no affinity for α 1 adrenergic and H1 antihistaminic receptors. Tianeptine can be considered as the mid-position antidepressants. Defrance et al. [45] have shown that tianeptine does not show any affinity for the muscarinic receptors. Tianeptine has been reported to exert little toxicity such as gastralgia, abdominal pain, dry mouth, anorexia, nausea, vomiting, flatulence, insomnia, drowsiness, nightmares, asthenia, and tachycardia in certain patients [44-46]

Phytochemicals as antidepressants

Some phytochemicals are reported to act as antidepressants. These chemicals present in the plant extracts are expected to be safer and more cost effective than the existing antidepressants. Different ethno-pharmaceutical properties of various plant extracts and their effects are summarised in Table 7.

Table 7: Phytochemicals acting as natural antidepressants.

Plant Extract	Common Name	Part used from the Plant	Type of Extract, Compound, Doses	Effects	References
Allium macrostemon	Chinese Garlic	Bulb	Water Extracts	Behavioural Despair	[47]
Allium sativum	Garlic	Rhizome	Ethanollic Extract, dose- 25,50 and 100 mg/kg		[48]
Aloysia polystachya	Lemon Verbena	Aerial Part	Hydroethanollic Extract	Effect on Depression	[49]
Apocynum venetum	Dogbane	Aerial Part	Dose-30-125 mg/kg		[50]
Areca catechu	Betel Nut	Fruit	Ethanollic Extract, dose- 4-80 mg/kg	Effect on Motor Activity	[51]
Asparagus racemosus	Satavari	Root	Methanollic Extract, dose- 100,200 and 400 mg/kg	Effect on Serotonergic And Noradrenergic System And Augmentation Of Antioxidant Defences	[52]
Bacoba monnieri	Brahmi	Aerial Part	Methanollic Extract, dose- 20 and 40 mg/kg	Significant Antioxidant Effect, Anxiolytic Activity And Improve Memory Retention	[53]
Berberis aristata	Indian Barberry	Root	Berberine, (An Alkaloid), dose-5,10 and 20 mg/kg.	Effect on CNS, Inhibit Monoamine Oxidase-A	[54]
Bupleurum falcatum	Chai Hu, Hare's Ear Root	Root	Methanollic Extract	Psycho stimulant Effect	[55]
Cimicifuga racemosa	Black Bugbane	Roots And Rhizomes	Ethanollic And Isopropanollic Aqueous Extracts	Effect on heraprutical Responses In Climacteric Women	[56]

Clitoria ternatea	Butterfly Pea	Root ,Bark	Ethanollic Extract, 50 or 100 mg/kg	Effect on Cognitive Behaviour, Anxiety, Depression, Stress	[57]
Crocus sativus	Saffron	Stigma	Ethanollic Extract	Effect on Depression	[58]
Curcuma longa	Turmeric	Rhizome	Aqueous Extract, dose- 140-560 mg/kg for 14 days.	Mao Inhibition In Brain	[59]
Emblica officinalis	Amla	Fruit	-	Effect on Psychiatric Disorder	[60]
Ginkgo biloba	Ginkgo, Maidenhair Tree	Leaves	Lipophilic Extract, dose- 50 and 100 mg/kg	Act As Anti-Stress and Antidepressant	[61]
Glycyrrhiza uralensis	Mulethi	Root	Liquiritin (Flavones)	Antidepressant Like and Antioxidant Activity By Measuring Erythrocyte Superoxide Dismutase (Sod) Activity And Plasma Malondialdehyde (MDA) Level	[62]
Glycyrrhiza glabra	Mulethi	Root	Aqueous Extract, Liquorice Extract	Effect on Inhibition Of Mao	[63]
Hippeastrum vittatum	Amaryllis	Flower	Alkaloids	Effect on Neurological Disorders And Neuro degenerative Disease	[64]
Hypericum canariensel. And Hypericum glandulosum	Canary Island St John Wort	Aerial Part	Methanolic Extract	Neuro pharmacological Effect, Helps In Muscle Relaxation, Anti-cholinergic And Sedative Properties	[65]
Hypericum reflexum	Hypericum	Aerial Part	Methanolic Extract	Effect on CNS	[66]
Kaempferia parviflora	Kava Kava	Kava Root/ Rhizome	Rhizome Extract	Effect on Psychiatric Illness	[67]
Lafoensia pacari	Didal	Leaves	-	Effects on CNS	[68]
Magnolia bark and ginger rhizome	Magnolia, Ginger	Bark, Rhizome	Honokiol and Magnolol, Polysaccharides	Effect on Synergistic Interaction	[69]
Marsilea minuta	Dwarf Water Clover	Root	Marsiline, Sedative And Anticonvulsant Property	Effect on Insomnia And Other Mental Disorders	[70]
Mimosa pudica	Sensitive Plant	Leave	Aqueous Extract	Act As Tricyclic Antidepressants	[71]
Mitragyna speciosa	Kratom	Leaves	Mitragynine An Active Alkaloid	Effect on Diarrhea, Diabetes And Improve Blood Circulation	[72]
Momordica charantia	Bitter Gourd / Bitter Melon	Fruit	Methanol Extract, dose- 300mg/kg		[73]
Morinda officinalis	Indian Mulberry	Root	Dose- 25-50 mg/kg	Effective In Response Rate	[74]
Oscimum sanctum	Tulsi	Aerial Part			[75]

<i>Paeonia lactiflora</i> pall	Garden Peony	Root	Ethanol extract, dose- 250 and 500 mg/kg	Effect on Central Monoaminergic Neurotransmitter System	[76]
<i>Piper laetispicum</i>	Piper	Stem And Root	Amide (Alkaloid), dose- 2mg/kg	Antinociceptive Properties, Effect on Pain And Depression	[77]
<i>Piper tuberculatum</i>	Black Pepper	Fruit	Piplartine (An Amide) , dose- 50 and 100 mg/kg	Effect on Anxiolytic And Antidepressant Activities, Anxiety And Depression.	[78]
<i>Polygala sabulosa</i>	Polygala	Aerial Part	Scopoletin, A Coumarin	Effect on Serotonergic, Dopaminergic And Noradrenergic Systems	[79]
<i>Rhazyastricta</i>	White Henna	Leaves	Aqueous Extract	Effect on Monoamine Oxidase Inhibition	[80]
<i>Rosmarinusofficinalis</i>	Rosemary	Fresh Juice	Hydro-alcoholic Extract	Interaction With The Monoaminergic System	[81]
<i>Salvia elegans</i>	Pineapple Sage	Leave	Hydroalcoholic Extract	Putative Anxiolytic	[82]
<i>Schinusmolle</i> L	Peruvian Pepper Tree	Leaves	Hexenic Extract	Pharmacological Effects, atleast At A Preclinical Level	[83]
<i>Siphocampylus verticillatus</i>	Siphocampylus	Aerial Parts	Hydroalcoholic Extract , dose range-100-1000 mg/kg	Interaction With Adrenergic, Dopaminergic, Glutamatergic And Serotonergic System	[84]
<i>Sphaeranthu sindicus</i>	East Indian Globe Thistle	Whole Part	Hydroalcoholic Extract	Effect On Anxiety, Depression And Convulsions	[85]
<i>Tabebuia avellaneda</i>	Lapacho, Taheboo Tree	Bark	Ethanol extract	Effect Of The Association Of The Extract With The Antidepressants	[86]
<i>Tagetes lucida</i>	Marigolds	Aerial Part	-	Effect On CNS	[87]
<i>Tinospora cardifolia</i>	Guduchi	Whole Part	Petroleum Ether Extract, dose- 50, 100 and 200 mg/kg.	Effect on Mao-A and Mao-B	[48]
<i>Valeriana officinalis</i>	Valerian	Root	Ethanol extract	Effect on Mild Sleep Disorders and Nervous Tension	[48]
<i>Valeriana wallichii</i>	Indian Valeriana	Root Bark	Methanolic and Aqueous Extract		[89]
<i>Withania somnifera</i>	Ashwagandha	Aerial Part	Bioactive Glyco withanolides	Effect on Anxiolytic And Antidepressant Action	[90]

Conclusion

Depression is a serious psychological condition but it can be effectively treated with available therapies. The stock of antidepressants available may be selectively used for treating depression safely without any side effects. The right medication to an individual depends on the clinico-physiological conditions of the patient such as symptoms, possible side effects, and interaction with other medications, state of pregnancy or breast feeding and the mental conditions. Different classes of antidepressants are in practice depending on the type and requirement of depression. Antidepressants include selective serotonin reuptake inhibitors (SSRIs), Serotonin and norepinephrine reuptake inhibitors (SNRIs), Norepinephrine and dopamine reuptake inhibitors

(NDRIs: Bupropion (Wellbutrin, Aplenzin, Forfivo XL), Atypical antidepressants (trazodone (Oleptro), mirtazapine (Remeron) and vortioxetine (Brintellix)), Tricyclic antidepressants (imipramine (Tofranil), nortriptyline (Pamelor), amitriptyline, doxepin, trimipramine (Surmontil), desipramine (Norpramin) and protriptyline (Vivactil)), Monoamine oxidase inhibitors (MAOIs: tranylcypromine (Parnate), phenelzine (Nardil) and isocarboxazid (Marplan)) and other medications such as mood stabilizers or antipsychotics all as well as anti-anxiety and stimulant medications. Many of these medications have their side effects. It could be however worthwhile to investigate the plant based principles to be used as more effective and safe chemotherapeutic compared to the currently used synthetic regimen.

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