Depression is a common mental disorder and one of the most important causes of disability in the world, with a heavy social burden and a substantial lifetime risk (WHO, 2010), as high as 20% (Kessler et al., 2005). Depression is frequently recurrent and chronic, and it has been associated with suicide risk and psychosocial dysfunction (Emslie et al., 2005). Symptoms of depression include depressed mood, loss of pleasure, inability to concentrate, lack of energy, dysregulated sleep or appetite, feelings of worthlessness or guilt, and thoughts of suicide. In addition to the personal suffering and loss associated with depression, the high incidence and chronic nature of depressive illness result in a significant public health burden. This is estimated to be tens of billions of dollars each year for the United States, largely due to loss of productivity in the workplace (Wang et al., 2003). The public health impact of depression is partially due to the fact that available treatments are suboptimal.

Antidepressant therapy include drugs with exceptional structural chemical diversity. According to the most accepted hypothesis of depression, the monoamine theory, the major neurochemical process in depression is the impairment of monoaminergic neurotransmission and the decrease in extracellular concentrations of noradrenaline and serotonin (Schildkraut, 1965; Hindmarch, 2002; Kiss, 2008). Recently, oxidative stress is closely correlated with depression. Increased lipid peroxidation (LPO) has been reported in depressed patients (Galecki et al., 2009; Sarandol et al., 2007) and decreased antioxidant enzyme levels in depressed patients is reported (Ng et al., 2008; Sarandol et al., 2007) and preclinical studies have suggested that antioxidants have antidepressant properties (Eren et al., 2007; Zafir et al., 2009). The reactive oxygen species (ROS) like hydroxyl radicals, superoxide anion, hydrogen peroxide and nitric oxide, produced during normal cellular metabolic functions, produce oxidative damage in brain (Coyle and Puttfarken, 1993; Frei, 1994). The brain is more
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vulnerable to oxidative stress because of its elevated consumption of oxygen and the consequent generation of large amounts of ROS.

Tricyclic antidepressants (TCA) and monoamine oxidase inhibitors (MAOI) are used as antidepressants from several decades. TCA’s have class specific limitations like antimuscarinic effects, arrhythmias, causes severe sedation and hypotension which interfere with the quality of life. Similarly, MAOI’s cause hypertensive crisis with tyramine containing foods. This led to the development of the selective serotonin reuptake inhibitors (SSRIs) and Serotonin norepinephrine reuptake inhibitors (SNRIs) that are widely used today. The SSRIs and SNRIs have improved safety and side-effect profiles compared to the older drugs, but the primary mechanisms are similar, the therapeutic efficacy and the drawbacks (slow therapeutic onset, high remission rates, and treatment resistant patients) are also similar (Nestler et al., 2002; Sonawalla and Fava, 2001).

Improvement of therapeutic options (especially designing treatments for patients that do not respond to currently available drugs) depends on the identification of underlying pathological processes in depression and potential mechanisms for their reversal. 30% of depressive patients do not react appropriately to the first-line treatment (Fava and Rush, 2006). Thus, the search for more efficacious and well-tolerated drugs is in progress. The need for the discovery and development of new pharmaceuticals for the treatment of depression demands that all approaches to drug discovery be exploited. Among the possible approaches, the use of natural products has made many unique and vital contributions to drug discovery (Newman et al., 2003).

The antidepressant drugs used in the clinic today have heterogeneity in the therapeutic response, side effects and high economic cost. Furthermore, treatment of depression with conversional antidepressant drugs provides a complete remission in 70% of the individuals
treated (Fava and Rush, 2006). Therefore, the study of the antidepressant-like effects of herbs is an increasing interest (Newman et al., 2003). Medical therapies with plants may be effective alternatives in the treatment of depression, and the research of their effects has progressed significantly since the past decade (Hasrat et al., 1997a,b).

The use of natural products with therapeutic properties is as ancient as human civilization and for a long time, mineral, plant and animal products were the main source of drugs. Herbs are used for revitalizing body systems and in the treatment of diseases in almost all ancient civilizations. The Rigveda, which is the oldest book of library of man, supplies the information of some herbs. In recent years the use of information in traditional medicinal plant research has again received considerable interest. Plants represent the second largest source of biodiversity, India is represented by rich natural biodiversity and offers a unique opportunity for drug discovery researchers. The country is blessed with two hot spots (Eastern Himalayas and Western Ghas), out of the world’s 18 hotspots of plant biodiversity and is 7th among the 16 Mega diverse countries, where 70% of the species occur collectively. Over 7500 plant species have been reported to be used in the Indian traditional systems including ethnno medicines (Chistokhodova, 2002). Out of 20,000 to 55,000 plant species used globally, only a small portion has been investigated for medicinal purposes. About 25% of the drugs prescribed world wide have plant origin. Out of the 252 drugs considered as essential drugs by the WHO, 11% are exclusively of plant origin and a significant number of synthetic drugs obtained from natural precursors (Rates, 2001). Quinine, reserpine, tubocurarine, vincristine, vinblastine, pilocarpine, atropine, morphine, cocaine, taxol are some of the plant derived drugs which do not have replacement even today. Even today, only 15-20% of terrestrial plants have been evaluated for pharmaceutical potential.
Nowadays, because of a prevalent belief that “natural is better”, complementary and alternative medicines are widely used by patients, even among those taking prescription drugs (Hunt et al., 2010). A number of herbs and dietary supplements have demonstrable effects on mood, memory, insomnia and jaded appetite. As a result, psychiatric conditions especially depression were among the most common conditions treated with complementary and alternative therapies (Astin, 1998; Hunt et al., 2010). The antidepressant effect of herbs has been paid more and more attention because of increasing incidence of depression and predominance of traditional herbs in therapy (Wong and Licinio, 2004; Sanchez-Mateo et al., 2005; Zhou et al., 2011). As for any antidepressant screening test, essential requirement is accurate prediction about antidepressant activity, with such characteristics as cheapness, robustness, reliability and easy to use (Mitchell, 2005).

*Argyreia nervosa, Jasminum sambac, Passiflora foetida* and *Sapindus emarginatus* are commonly used in folk remedies against depression. However, its neuropharmacological mechanism on antidepressant like action is unknown. Thus, it is necessary to investigate the mechanism of herbs that consumers usually use. The preliminary phytochemical analysis reveals that the hydroalcoholic extract of *Argyreia nervosa* showed positive results towards alkaloids, tannins, phenolic compounds, flavonoids, sterols, lignans, sugars; *Jasminum sambac* showed positive results towards tannins, phenolic compounds, flavonoids, triterpenoids, sugars, coumarins; *Passiflora foetida* showed positive results towards alkaloids, tannins, glycosides, phenolics, flavonoids, sterols, sugars, lignans; *Sapindus emarginatus* showed positive results towards tannins, phenols, glycosides, sterols, triterpenoids, saponins, sugars, lignans, which was confirmed by TLC and HPTLC studies. The phytoconstituents were isolated by column chromatography and structure was elucidated by spectral studies.
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Argyreia nervosa, Jasminum sambac, Passiflora foetida and Sapindus emarginatus were found to have potent antioxidant activity, as evident from invitro antioxidant studies against DPPH, Nitric oxide, Hydrogen peroxide scavenging activities, Reducing power assay, Total antioxidant capacity indicating that AN, JS, PF and SE were effective in scavenging the ROS generated during major depressive disorder. It is important to scavenge the ROS which is one of the therapeutic target in treating depression (Evans, 1993).

The present study is the first, to our knowledge, to show antidepressant-like activity produced by Argyreia nervosa, Jasminum sambac, Passiflora foetida and Sapindus emarginatus, as determined by the forced swimming test (FST), tail suspension test (TST).

Tail suspension test and forced swim test are the widely used animal models of depression for the screening of antidepressive activity (Porsolt et al., 1977c; Steru et al., 1985). The forced swimming and tail suspension-induced state of immobility in animals claimed to represent a condition similar to human depression and amenable to reversal by antidepressant drugs (Renard et al., 2003). These animal models were based on the despair or helplessness behavior to some inescapable and confined space in animals and are sensitive to various antidepressant drugs. Considering that the TST is commonly used to detect and characterize the efficacy of antidepressant drugs and possesses greater sensitivity than the FST (Steru et al., 1987). FST induced a state of “hopelessness” and/or “abandonment” in mice that was analogous to those showed by depressed people. It has been demonstrated that antidepressant drugs reduce this behaviour of abandonment in mice (Castagne et al., 2001). In addition, several extracts from plants have been evaluated in this model with positive results (Chen et al., 2005; Sanchez-Mateo et al., 2007; Machado et al., 2009). Animals are placed in an inescapable situation and the antidepressant-like activity is expressed by the decrease of immobility when compared with control groups.
The FST involves placing a rat or mouse in a cylinder with enough water so that it cannot touch the bottom with its hind paws (Porsolt et al., 1977a,b, 1978). A normal animal will show an immediate burst of activity, try to escape, and then eventually adopt an “immobile” posture, where it will make only those movements necessary to keep its head above water. The development of immobility is facilitated by prior exposure to the test and a 24-h prior preexposure to the test is often used (Porsolt et al., 1978). Immobility is quantified during brief test periods and classical antidepressants such as the monoamine oxidase inhibitors, tricyclics, and atypical antidepressants all decrease the duration of immobility in rats and mice in a dose-dependent manner (Borsini and Meli, 1988; Porsolt et al., 1977a,b). A modified FST procedure is often used in rats that allows behavior in response to norepinephrine-selective drugs to be distinguished from serotonin-selective antidepressants. The modification involves separately quantifying the predominant active behaviors as either swimming or climbing. Swimming behavior predominates for serotonergic antidepressants and climbing predominates for drugs that are primarily noradrenergic, allowing the FST to detect this distinction (Detke et al., 1995; Lucki, 1997). The FST may yield false positive results with drugs that increase locomotor activity, and correspondingly, decrease immobility (e.g., amphetamine).

The TST is conceptually similar to the FST and is suggested to have greater sensitivity. A mouse is suspended by the tail in this test and observed for the extent of immobility versus active movement (Steru et al., 1985). Similar to the FST, the TST is also based on the adoption of a passive response in a stress situation. Acute antidepressant treatment given prior to the test reduces immobility time in the TST and it is considered to have good predictive validity (Cryan et al., 2005; Perrault et al., 1992; Steru et al., 1985). Although conceptually similar, the TST and FST do not show identical sensitivities to
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pharmacologic agents or to strain differences, suggesting that responding in these tests may be determined by nonidentical substrates (Bai et al., 2001). Different mouse strains respond differently to basal immobility in the TST, indicating that this test is sensitive to genetic influence (Ripoll et al., 2003). Differential sensitivity between strains for antidepressant response is suggested to be related to variations in monoamine levels (Ripoll et al., 2003). The TST is used only in mice and not in rats due to their larger size and weight. The TST has similar limitations to the FST, including a false positive response to psychostimulants and acute drug response.

The FST and TST have been used extensively for screening of antidepressant like drugs, but the selectivity of these tests for monoamine-based mechanisms may limit their ability to detect novel mechanisms (Lucki, 1997; Thiebot et al., 1992; Weiss and Kilts, 1995; Willner, 1990).

In the present study we provided convincing evidence that the extracts administered by oral route produces a specific antidepressant-like effects in TST and FST after 7 days treatment. The results presented here show that extracts at 250 and 500 mg/kg lead to a significant reduction in the immobility period after 7 days treatment in TST in a dose-dependent manner. In the present study we used mouse as animal and utilized FST and TST for the evaluation of antidepressant activity of selected plants. AN showed increased swimming, whereas JS, PF and SE showed increased climbing. All four selected plants showed decreased immobility in FST and TST. In our study, none of extracts tested increased locomotor activity at doses that produced antidepressant-like effect, indicating that the specific actions of this extract on the behavioral model are predictive of antidepressant activity. Although both TST and FST are similar in their constructs and objectives, they are different in terms of the biological substrates that underlie the observed behaviour (Bai et al.,
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2001; Cryan et al., 2005). To avoid false positive results in the FST and TST, it is important to rule out the possibility that reductions in the immobility time were not merely a result of the psychostimulant effects of the extract (Martínez-Mota et al., 2008). However, swimming behavior predominated with AN and climbing behavior predominated with JS, PF and SE in the FST indicating the involvement of serotenergic system in the mechanism of action of AN and noradrenergic system in the mechanism of action of JS, PF and SE. Swimming behavior predominates for serotonergic antidepressants and climbing predominates for drugs that are primarily noradrenergic, allowing the FST to detect this distinction (Detke et al., 1995; Lucki, 1997).

It is well accepted that increasing brain monoamine neurotransmitters is an effective way to treat depression (Delgado and Moreno, 1999; Xia et al., 2007). The dysregulation of the neurotransmitters noradrenaline, serotonin and dopamine has been suggested to play a role in the pathogenesis of depression (Schildkraut, 1965; Coppen, 1967). Generally, the most widely accepted hypothesis of the biological basis of depression implicate 5-HT and noradrenaline system dysfunction. In our study, we detected the brain monoamine levels by HPLC- EC detector. The serotonergic system is intimately linked to stress and anxiety responses (Graeff et al., 1996). Besides the well-established role of the serotonergic system in the pathogenesis of depression this system is also a target for the conventional pharmacotherapy (Duman et al., 1997; Wong and Licinio, 2001). In parallel with the serotonergic system, experimental and clinical studies indicated that the noradrenergic system is strongly implicated in the pathophysiology of depression (Brunello et al., 2003; Nutt, 2006).

Depression is also associated with a hypofunction of the noradrenergic system. In the present study, to probe the mechanism of action of AN, JS, PF and SE, the effect of these
extracts was studied on the brain NE, DA, 5HT levels and on the activity of MAO-A and B and on indicators of oxidative stress (GSH, MDA, Vit C). JS and PF at higher dose of 500mg/kg significantly increased the NE and DA without alteration in the activity of MAO-A and MAO-B indicating the increase is not due to the inhibition of metabolism, but due to increased synthesis.

This strengthens the involvement of noradrenergic system and confirms the results of increased swimming time in FST. Of the all the four plant extracts only SE was effective at lower dose 250 mg/kg as well, in addition to higher dose of 500 mg/kg. SE significantly increased the level of DA and NE with a significant decrease in the activity of MAO-A indicating increased NE is due to increased synthesis as DA levels are increased simultaneously with decreased metabolism as MAO-A activity is decreased. In addition there was no inhibition of MAO-B activity, indicating raise in DA is not due to inhibition its metabolism.

The dopaminergic system is also an important target implicated in the regulation of depression (Klimek et al., 2002). DA has many functions in the brain, including important roles in behavior and cognition, punishment and reward, sleep, mood, attention and learning (Arias-Carrion and Poppel, 2007; Dunlop and Nemeroff, 2007). A number of studies consistently reported a low DA and/or DA metabolite levels in patients with depressive illness (Hamner and Diamond, 1996; Lambert et al., 2000). The deficit of DA levels in depression has also been proved by an index of acute tyrosine depletion (Ainsworth et al., 1998), which resulted in reduced brain DA synthesis (Mc-Tavish et al., 1999). In addition, it was demonstrated that chronic treatments with antidepressants such as amineptine improved the dopaminergic neurotransmission, which contribute to therapeutic effect of these drugs (Papakostas, 2006). Online with this in the present study JS, PF and SE increased the DA levels on par with standard drug imipramine, indicating the involvement of dopaminergic
system in part in the antidepressant activity of these extracts on one hand on the other may be 
these increased DA levels responsible for the increase in NE levels as DA is precursor for the 
NE synthesis.

AN at higher dose of 500mg/kg significantly increased the level of 5HT without 
significant decrease in the activity of MAO-A indicating the increase was not due the 
inhibition of metabolism, indicating AN’s antidepressant activity in part due to increased 
synthesis of serotonin.

Exact mechanisms underlying the antidepressant action cannot be concluded at the 
moment due to the presence of large number of phytochemicals in the AN, JS, PF and SE. 
However, the antidepressant activity may be attributed to the presence of tannic acid, 
polyphenols in part by attenuation of oxidative stress produced during depression. This also 
rules out the significant role of Flavonoids as SE showed the potent antidepressant activity 
amongst the four which is devoid of any Flavonoids. SE showed highest tannic acid content 
(71.42± 0.24 mg/g). Further this was the only extract among the four extracts showed 
MAO-A inhibitory activity. The result of inhibition of MAO-A also confirms that MAO-A 
may be more sensitive to tannic acid than MAO-B. Tannic acid has been shown to be a non 
selective inhibitor of monoamine oxidase, thereby increasing the levels of monoaminergic 
neurotransmitters in the brain (Dar and Khatoon, 1998). AN also had the tannic acid content 
(63.08± 1.23 mg/g) but it did not show significant MAO-A inhibitory activity. This 
indicates, may be the minimum effective dose required is more than the amount present in 
AN. However, the other two plants had least amounts of tannic acid equivalents (JS-16.08± 
1.57 mg/g; PF 16.11± 0.96 mg/g), justifies the absence of MAO inhibitory activity.

Lipid peroxidation (LPO), an index of oxidative stress, damages the cell membrane 
(membrane fluidity, receptors, and ion channels) (Mattson, 1998), which may result in
calcium influx and cause cell death. In the depressed animal models (FST) as well decrease in antioxidants and increase in lipid peroxidation was observed. In the present study also depressed rats showed increased lipid peroxidation and decreased reduced glutathione (GSH) and Vit C. The increased level of LPO observed in depressed (control) rats, indicates an excessive formation of free radicals and activation of LPO system. Interestingly, our results evidenced a parallel increase in GSH, the most important antioxidant in response to treatment with extracts in depressed animals. The increase in activity may provide an effective defense from the damaging effects of not only superoxide anion and hydrogen peroxide but also from damaging and highly reactive hydroxyl radical generated by Fentons reaction of the former radicals (Winterbourn, 1995). In the present study, depressed animals (control) showed increased LPO and decreased GSH and Vitamin C levels. Thus, antidepressant like activity of extracts might be in part due to inhibition of lipid peroxidation.

The acute toxicity studies were conducted as per the OECD guidelines 420, where the limit test dose of 2000 mg/kg was used. No test substance-related mortality was observed at 2000 mg/kg. So, testing at higher dose mayn’t be necessary and the compound was said to be practically non-toxic (Gosh, 1984). The alcoholic extract of AN, JS, PF, and SE at a dose of 250 and 500mg/kg orally daily for 28 days did not produce any sign of observable toxicity during the experimental period. All the tested Haematological parameters such as Hb, RBC, WBC and PCV; Liver function parameters like ALT, AST, ALP; Kidney function parameters like urea, blood urea nitrogen, creatinine; metabolic indices like LDL, HDL, VLDL, TG, Glucose and Liver, Heart, Lung, Spleen, Kidney and Body Weight were within the normal range.

Generally, the reduction in body weight gain and internal organ weights is a simple and sensitive index of toxicity after exposure to toxic substances (Raza et al., 2002; Teo et al.,
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In subacute toxicity study rats treated with 250 and 500 mg/kg doses of ethanol extract of AN, JS and PF had a progressive weight in body and organs. The increase in weight was not significantly different from that of the control. The progressive increase in body weight and organ weight at dose of 250 and 500 mg/kg of rats during 28 days of administration of hydroalcoholic extracts indicate the improvement in the nutritional state of the animal. The growth response effect could be as a result of increased food and water intake. The calculated relative weight of the control and treated animal groups varied from one organ to other, no significant differences were noted in the relative weight of other organ (liver, heart, lung, spleen and kidney). However there was no correlation between relative weight of the organs and the various doses of the extracts administered. The haematological status after 28 days of oral administration of extracts was also assessed. In general the results showed that the values for the RBC and WBC were slightly increased in groups compared to the control. However no significant variation for RBC, WBC, Hb and PCV were observed.

The small transient of values observed in blood hematology did not show any dose responsiveness. Nevertheless, all values lay within the normal limits. AN, JS, PF and SE did not show any significant reduction of normal blood glucose. The extracts did not induce any damage to the kidney and liver as examined by clinical blood chemistry. ALT and AST are two liver enzymes that are associated to the hepatocellular damage. Although both AST and ALT are common liver enzymes because of their higher concentrations in hepatocytes, only ALT is remarkably specific for liver function since AST is mostly present in the myocardium, skeletal muscle, brain and kidneys (Sacher and Mepherson, 1991). No significant changes were observed in ALT, AST and ALP activities in the serum of rats. In other parameters like Urea and Blood Urea Nitrogen (BUN) there was no significant changes observed. A mild elevation of AST level has been shown to be associated with liver injury or myocardial infarction.
The higher the activity of AST has been observed in larger infarction size (Feldman and Zinkl, 2000). A typical myocardial infarction gives an AST/ALT ratio greater than 1 while an AST/ALT ratio less than 1 is a result of release of ALT from the affected liver (Sacher and Mepherson, 1991), AST /ALT of more than 2 indicates alcoholic hepatitis or cirrhosis (Sacher and Mepherson, 1991). These results indicated that the extracts when taken for long periods of time might not cause liver disease. Furthermore, gross examination of internal organs of all the rats revealed no detectable abnormalities. In conclusion, this study presents strong evidence of the nontoxic effect of the extracts. These results showed that the use of extracts of AN, JS, PF and SE was safe and supports the traditional use of these plants in folk medicine.