STUDIES ON THE NEUROPHARMACOLOGICAL PROPERTIES OF THE METHANOLIC EXTRACT OF *FICUS PLATYPHYLLA* STEM BARK.

BY

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A thesis submitted to the Postgraduate School, Ahmadu Bello University, Zaria, in partial fulfilment of the requirements for the award of the degree of Master of Science (Pharmacology).

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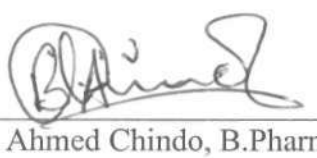
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DECLARATION

I hereby certify that the work reported in this Thesis was carried out by me in the Laboratories of the Department of Pharmacology and Clinical Pharmacy, Ahmadu Bello University, Zaria, and the Department of Pharmacology and Toxicology, National Institute for Pharmaceutical Research and Development, Abuja, under the joint supervision of Prof. K.S. Gamaniel and Dr. A. A. Odutola. The work of other Investigators is acknowledged and referred to accordingly. I solemnly declare that no part of this Thesis has been submitted elsewhere for a degree.



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DEDICATION

This thesis is dedicated to:

Jehovah LORD, the GOD of all flesh. He makes everything beautiful for me at the appointed time.

And to my parents, brothers and sisters, for their love, care, patience, encouragement and moral support that motivated me towards academics. I consider this another stepping stone.

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Above all I give thanks to my GOD, for creating this stream in the desert for my sake. I pray that my eyes will always see his goodness and the words of my mouth will continually praise him.

ABSTRACT

Ficus platyphylla Del.-Holl (Moraceae) is a deciduous plant found mainly in the Savanna regions of West Africa. The plant is used traditionally in Northern Nigeria to treat depression and persons possessed by spirits *(bori, ciwon inna* or *iska).* A few reports (oral communication) suggest that the stem bark may contain some analgesic and sedative principles. The effects of the methanolic extract of *Ficus platyphylla* stem bark were studied on locomotor activity, pentobarbitone sleeping time, amphetamine induced hyperactivity and stereototyped behaviour, apomorphine induced stereotyped behaviour, catalepsy, pain, inflammation, electroshock and pentylenetetrazole-induced seizures in chicks, mice and rats. The LC50 and intraperitoneal LD50 of the extract were found to be 113.7µg/ml and greater than 2000mg/kg in brine shrimp and mice lethality studies respectively. The extract significantly exhibited a dose and time dependent decreased in spontaneous motor activity (SMA) and antagonised amphetamine induced stereotyped behaviour in mice. The extract exhibited an anti-inflammatory activity in a dose related maimer and significantly reduced the total mobile, static and rearing counts as well as the active and mobile times dose and time dependently. It also attenuated amphetamine induced hyperactivity, prolonged the duration of pentobarbitone induced sleep in rats, reduced the incidence of pentylenetetrazole induced seizures and protected the mice against tonic hind limb extension and death, but did not protect the chicks against electroshock seizure. The extract significantly attenuated apomorphine induced stereotyped behavioural patterns and acetic acid induced pain in a dose and time related manner. The extract induced a significant cataleptogenic effect and exacerbated haloperidol induced catalepsy. The results suggest the presence of

pharmacologically active principles in the extract of *Ficus platyphylla* with profound sedative activity. The data provide scientific evidence for the use of the plant in traditional medicine for psychotic states (since there is evidence that the active principles exhibited properties that were similar to clinically useful drugs against laboratory models of psychoses).

TABLE OF CONTENTS

TITLE	PAGE
Title Page	i
Certification	ii
Declaration	iv
Dedication	v
Acknowledgement	vi
Abstract	viii
Table of Contents	x
List of Tables	xiv
List of Figures	xv
Abbreviations	xvi
CHAPTER ONE	
1.0. LITERATURE REVIEW	1
1.1. Organisation of the Central Nervous System	1
1.2. Function of Specific Areas of the Brain and Spinal Cord	2
1.2.1. Cerebral Cortex	2
1.2.2. Limbic System	3
1.2.3. Brain Stem (Midbrain, Pons and Medulla)	4
1.2.4. Cerebellum	5
1.2.5. Spinal Cord	5
1.3. Drugs Acting on the Central Nervous System	6
1.3.1. Antipsychotic Drugs	7
1.3.2. Antianxiety Drugs	13

1.3.3. Antidepressants.....15

1.3.3.1. Tricyclic Antidepressants.....18

1.3.3.2. Monoamine Oxidase Inhibitors.....20

1.3.4. Antimanic Agents.....22

1.3.5. Hypnotics and Sedatives.....24

1.3.5.1. Benzodiazepines.....25

1.3.5.2. Barbiturates.....26

1.3.5.3. Aliphatic Alcohols.....27

1.3.6. Anticonvulsant Agents.....28

1.3.7. Drugs used in the Treatment of Parkinsonism.....31

1.3.8. Analgesics.....34

1.3.8.1. Narcotic Analgesics.....34

1.3.8.2. Non narcotic Analgesics.....36

1.3.9. Analeptics.....37

1.3.10. CNS Disorders and Medicinal Plants.....38

1.3.11. Objectives of the Study.....42

CHAPTER TWO

2.0. MATERIALS AND METHODS.....44

2.1. Plant Material.....44

2.2. Animals.....44

2.3. Chemicals and Drugs.....45

2.4. Equipment.....45

2.5. Phytochemical Tests.....46

2.6. Toxicological Studies.....46

2.6.1. Brine Shrimp Lethality Bioassay (LC_{50}).....46

2.6.2. Acute Toxicity Studies in Mice (LD_{50}) 47

2.7. Spontaneous Motor Activity Testing.....47

2.8. Studies on Amphetamine-induced Hyperactivity in Mice.....48

2.9. Studies on Amphetamine-induced Stereotype Behaviour in Mice.....48

2.10. Studies on Apomorphine-induced Stereotype Behaviour in Mice.....49

2.11. Studies on Pentobarbitone Sleeping Time in Rats.....49

2.12. Studies on Haloperidol-induced Catalepsy in Rats.....50

2.13. Seizure Studies.....51

2.13.1. Pentylenetetrazole-induced Convulsion (Seizures) in Mice.....51

2.13.2. Electroshock induced Convulsion (Seizures) in Chicks.....51

2.14. Studies on the Analgesic Effect of the Extract in Mice.....52

2.15. Studies on the Anti-inflammatory Effect of the Extract in Rats.....52

2.16. Statistical Analysis.....53

CHAPTER THREE

3.0. RESULTS.....54

3.1. Brine Shrimp Lethality Bioassay (LC_{50}) 54

3.2. Acute Toxicity Studies in Mice (LD_{50}) 54

3.3. Effects of the Extract on Spontaneous Motor Activity in Mice.....54

3.4. Effects of the Extract on Amphetamine-induced Hyperactivity in Mice.....55

3.5. Effects of the Extract on Amphetamine -induced Stereotype Behaviour in Mice.....55

3.6. Effects of the Extract on Apomorphine-induced Stereotype Behaviour in Mice.....55

3.7. Effects of the Extract on Pentobarbitone -induced Sleep in Rats.....56

3.8. Effects of the Extract on Haloperidol-induced Catalepsy in Rats.....56

3.9. Effects of the Extract on Pentylenetetrazole -induced Seizures in Mice.....56

3.10. Effects of the Extract on Electroshock-induced Seizures in Chicks.....56

3.11. Analgesic Effect of the Extract on Acetic Acid -induced pain in Mice.....57

3.12. Anti-inflammatory Effect of the Extract in Rats.....57

CHAPTER FOUR

4.0. DISCUSSION.....79

REFERENCES.....86

LIST OF TABLES

		PAGE
Table 1:	Lethal Dose (LD_{50}) of the extract in mice.	58
Table 2:	Effects of the extract on the Spontaneous Motor Activity in mice. Gross activity recording from LETICA cage (LE 886)	59
Table 3:	Effects of the extract on locomotor activity in mice. Gross activity recording from AM 1051 Data logger.	61
Table 4:	Effects of the extract on amphetamine induced hyperactivity in mice. Gross activity recording from LETICA (LA 886).	62
Table 5:	Effects of the extract on amphetamine-induced stereotype behaviour in mice.	64
Table 6:	Effects of the extract on apomorphine induced stereotype behaviour in mice.	66
Table 7:	Effects of the extract on pentobarbitone sleeping time in rats.....	68
Table 8:	Effects of the extract on haloperidol induced catalepsy in rats.....	70
Table 9:	Effects of the extract on pentylenetetrazole induced seizures in mice.....	73
Table 10:	Effects of the extract on electroshock convulsion in chicks.....	74
Table 11:	Analgesic effect of the extract in mice.....	75
Table 12:	Anti-inflammatory effect of the extract in rats.....	77

LIST OF FIGURES

		PAGE
Figure 1:	Effects of the extract on Spontaneous Motor Activity in mice.....	60
Figure 2:	Effects of the extract on amphetamine induced hyperactivity in mice.....	63
Figure 3:	Effects of the extract on amphetamine induced stereotype behaviour in mice.....	65
Figure 4:	Effects of the extract on apomorphine induced stereotype behaviour in mice.	67
Figure 5:	Effects of the extract on pentobarbitone sleeping time in rats.....	69
Figure 6:	Effects of the extract on haloperidol induced catalepsy in rats.....	71
Figure 7:	Cataleptic effect of the extract in rats.....	72
Figure 8:	Analgesic effect of the extract in mice.	76
Figure 9:	Anti-inflammatory effect of the extract in rats.....	78

ABBREVIATIONS

ATPase	-	Adenosine Triphosphatase
ABU	-	Ahmadu Bello University
BDZs	-	Benzodiazepines
Ca^{++}	-	Calcium ions
cm	-	Centimetre
CNS	-	Central Nervous System
Co.	-	Company
CSF	-	Cerebrospinal Fluid
DA	-	Dopamine
ECT	-	Electroconvulsive Therapy
ed(s)	-	Editor(s)
EEG	-	Electroencephalogram
F.P	-	*Ficus Platyphylla*
Fig.	-	Figure
g	-	Gramme
GA	-	Genreral Anaesthetics
GABA	-	Gama Amino Butyric Acid
5HTAA	-	5-Hydroxy Indole acetic acid
Inc.	-	Incorporated
i.p.	-	Intraperitoneal
K^{+}	-	Potassium ion

LC	-	Lethal Concentration
LD	-	Lethal Dose
<	-	Less than
Li^+	-	Lithium ions
LSD	-	Lysergic acid diethylamide
m	-	Metre
MAOIs	-	Mono Amine Oxidase Inhibitors
µg	-	Microgramme
mg	-	Milligramme
min	-	Minute
ml	-	Millilitre
mm	-	Millimetre
NA	-	Nor adrenaline
NIPRD	-	National Institute for Pharmaceutical Research and Development.
PCPA	-	P-Chlorophenylalanine
PTZ	-	Pentylenetetrazole
REM	-	Rapid eye movement
SMA	-	Spontaneous Motor Activity
TCAs	-	Tricyclic Antidepressants.
µl	-	Microlitre
wks	-	Weeks
w/w	-	Weight per weight

CHAPTER ONE

CHAPTER ONE

1.0. LITERATURE REVIEW

Understanding the cellular and molecular organisation of the central nervous system (CNS) is essential for a proper elucidation of the sites and mechanisms of CNS disorders, and the way drugs can alter these functions. Knowledge about the anatomy, physiology and chemistry of the nervous system is not yet complete. Scientists are making fundamental and startling discoveries about brain function and dysfunction, and this has led to a better understanding of both the etiology and pathophysiology of many CNS disorders. Novel therapeutic agents are being developed for their management.

1.1. ORGANISATION OF THE CENTRAL NERVOUS SYSTEM

The nervous system provides the most important control and communication pathways in the body. It collects information from the internal and external environment, integrates them in the form of impulses and initiates appropriate responses. The brain and the spinal cord together constitute the central nervous system (CNS). The skull encases the brain while the spinal cord is contained within the vertebral canal (Backbone). The CNS is made up of simple interconnections of neurons, which coordinate and constantly modify motor functions according to sensory input, hormonal and other blood borne signals. It directs the traffic of information of different origins and destinations as if it were a single organ. In addition to the neurons, the nervous system contains numerous glial cells, which include microglia scavenger cells that enter the nervous system from the blood

vessels (Bloom, 1996). The oligodendrogliocytes are involved in myelin formation and the astrocytes are found throughout the brain and may send end-feet to the blood vessels. The glial cells have membrane potentials that vary with the external K^+ concentrations but do not generate propagated potentials. They produce substances that are trophic to neurons, and probably help to maintain the appropriate concentration of substance in the interstitial fluid by taking up potassium ions (K^+) and the neurotransmitters glutamate and gamma amino butyric acid (GABA) (Bloom, 1996). They are also responsible for the production of blood brain barrier in mammals. There are many steps in the transmission of messages from neurons to their target cells, and each step provides the potential for pharmacological, physiological and pathological interventions.

1.2. FUNCTION OF SPECIFIC AREAS OF THE BRAIN AND SPINAL CORD

1.2.1. Cerebral Cortex

The two cerebral hemispheres constitute the largest division of the brain. Regions of the cortex are classified by the anatomical positions (frontal, temporal, parietal and occipital), the modality of information processed (e.g. sensory, motor and association), and by geometrical relationship between cell types in the major cortical layers. The specialized functions of the cortical region arise from the interaction between a basic module of connections to and from other regions of the cortex (cortico-cortical systems) and non-cortical areas of the brain (sub-cortical systems). The association areas receive and process information from primary cortical sensory regions to produce higher cortical

functions such as abstract thought, memory and consciousness (Bloom, 1996). The cerebral cortices provide supervisory integration of the autonomic nervous system, somatic and vegetative functions, including those of the cardiovascular and gastro-intestinal systems (Miller, 1978). The control of blood pressure and gastric motility for example, may be susceptible to feed back control in human beings. Certain areas of the cortex are devoted to specific functions e.g. visual areas devoted to vision, and the motor area controls movement. (Tononi *et al.*, 1992).

1.2.2. Limbic System

This region sometimes referred to as the visceral brain consists of cortical tissue around the cerebral hemisphere and a group of associated deep structures, including the hippocampus, amygdaloid complex, septum, hypothalamus, olfactory and pyriform lobes, basal ganglia and parts of the thalamus. These structures lie beneath the cortical mantle and act in a complex manner to integrate emotional state with motor and visceral activities. The hippocampus is essential for learning and the formation of recent memory and this function is lost in patients with extensive bilateral damage to hippocampus or Alzheimer's disease, which destroys the intrinsic structure of the hippocampus (Zola-Morgan and Squire, 1993). The basal ganglia or neostriatum (The caudate nucleus, putamen, globus pallidus, and lentiform nucleus) form an essential segment of the extra-pyramidal motor system, which compliment the function of the pyramidal (or voluntary) motor system. Damage to the extra-pyramidal system inhibits the ability to initiate voluntary movements resulting to a group of disorders characterised by involuntary movements, such as tremors and rigidity of Parkinson's disease or the uncontrollable

limb movements of Huntington's chorea (Standaert and Young, 1996). The thalamus lies in the center of the brain beneath the cortex and basal ganglia, and above the hypothalamus. The neurons here act as relays between the incoming sensory pathways and the association areas as well as between the discrete and the association regions of the cerebral cortex. The thalamic nuclei and the basal ganglia also exert regulatory control over visceral function. Damage to the corpus striatum results in aphagia, adipsia and general sensory neglect. The hypothalamus forms the principal integrating region for the entire autonomic nervous system and it regulates, among other functions, body temperature, water balance, intermediary metabolism, blood pressure, sexual and circadian cycles, secretion of the adenohypophysis, sleep and emotion.

1.2.3. Brain Stem (Midbrain, Pons and Medulla)

This is sometimes referred to as the bridge portions of the CNS, which include the mesencephallon, pons, and medulla oblongata. They connect the cerebral hemispheres and thalamus-hypothalamus to the spinal cord. Most of the nuclei of the cranial nerves, as well as the major inflow and outflow tracts from the cortices and spinal cord are found in these bridge portions of the CNS. The reticular activating system is also found within these regions. The reticular activating system is an important region of gray matter that links peripheral sensory and motor events with higher levels of nervous integration. The major monoamine-containing neurons of the brain are found within this zone (Bloom, 1996). These regions together represent the points of central integration for coordination of essential reflexive acts such as swallowing, vomiting and those that involve the cardiovascular and respiratory systems. These areas also include the primary receptive

regions for most visceral afferent sensory information. The reticular activating system is essential for the regulation of sleep, wakefulness, and level of arousal, as well as for coordination of eye movement (Bloom, 1996).

1.2.4. Cerebellum

It arises from the posterior pons behind the cerebral hemispheres. The cerebella nuclei project to the motor cortex (by way of thalamus) and to the brainstem nuclei concerned with vestibular (position-stabilization) function. The cerebellum is generally regarded as playing an important role in the maintenance of appropriate body posture in space. In addition to maintaining the proper tone of antigravity musculature and providing continuous feedback during volitional movements of the trunk and extremities, the cerebellum may also regulate heart rate, possibly to maintain blood flow despite changes in posture (Bloom, 1996).

1.2.5. Spinal Cord

The spinal cord extends from the caudal end of the medulla oblongata to the lower lumbar vertebrae. Within this mass of nerve cells and tracts, the sensory information from skin, muscles, joints and viscera is locally coordinated with motor neurons and primary sensory relay cells that project to and receive signals from higher centers. The spinal cord is divided into anatomical segments (cervical, thoracic, lumbar and sacral) that correspond to divisions of the peripheral nerves and spinal column. Ascending and descending tracts of the spinal cord are located within the white matter at the perimeter of the cord, while inter-segmental connections and synaptic contacts are concentrated

within the H-shaped internal mass of gray matter. Sensory information flows into the dorsal cord, and motor commands exit via the ventral portion. Autonomic reflexes (e.g. changes in skin vasculature with alteration of temperature) can easily be elicited within local segments of the spinal cord, as shown by the maintenance of reflexes after the cord is severed (Lefkowitz *et al.,* 1996).

1.3. DRUG ACTING ON THE CENTRAL NERVOUS SYSTEM

A considerable number of prescriptions written today are for medications intended to affect the mental processes. They are mostly used to sedate, stimulate or otherwise change mood, thinking or behaviour. Many drugs used for other purposes also modify emotions and cognition either as part of their usual actions or as toxic effects of overdose. Generally, drugs, which interfere with the CNS functions, are either CNS depressants or CNS stimulants. CNS depressants include hypnotic-sedatives, simple aliphatic alcohols, general anaesthetics, anti-convulsants, analgesics etc. The CNS stimulants are the methylxanthines (e.g. caffeine, theophylline, and theobromine from tea, coffee, coca), amphetamine, cocaine, analeptics, (e.g. Pentylenetetrazole), antidepressants (MAOIs, TCAs), spinal cord stimulants (e.g. strychnine), etc. Agents that modify the functions of CNS do so by non-selective or selective mechanisms. Non-selective agents affect the neural axis in such a way that the highest centers involved in intellectual disintegration are dulled first. This is followed by loss of co-ordination at the motor and sensory levels, with the vital centers (controlling respiration and cardiovascular function) being most resistant (e.g. General anaesthetics, hypnotic sedatives, simple aliphatic alcohols etc). Selective agents produce effects upon one or

more CNS functions at doses, which have negligible actions on other neuronal responses (e.g. Antidepressants enhance mood without excitation or convulsion). Any drug that is capable of acting on the brain cells to change the mental process leading to sedation, stimulation or otherwise change of mood, thinking or behaviour is known to be psychotropic. These drugs affect the cortical, limbic and brainstem mechanisms that are of fundamental importance in the regulation of arousal, conciousness, affect and autonomic functions. Psychotomimetic drugs are employed experimentally to induce psychotic states for pharmacological analysis. Clinically they are important as drugs of dependence e.g. amphetamine. The class of drugs that will be considered below are those that are selective in their ability to modify symptoms of CNS disorders and are therefore employed clinically in the treatment of mental illnesses.

1.3.1. Antipsychotic Drugs

Psychoses are the most severe psychiatric disorders in which there is not only a marked impairment of behaviour but also a serious inability to think coherently, to comprehend reality, or to even gain insight into the abnormality. These conditions often include delusions and hallucinations, and thought processes may also be altered. Psychotic illnesses are characterised by disorders of thinking process as inferred from illogical and highly idiosynchratic communications, with disorganised or irrational behaviour and varying degrees of altered mood that can range from excited agitation to severe emotional withdrawal (Baldessarini, 1990).

The major varieties of psychotic disorders are organic (notably delirium and dementia) and idiopathic (primary functional) conditions. The organic conditions are typically associated with definable toxic, metabolic, or neuropathologic changes and are characterised by confusion, disorientation, memory disturbances and behavioural disorganisation. The underlying causes of the idiopathic disorders remain obscure; except in unusually severe stuporous states sometimes encountered in these illnesses, idiopathic disorders are charaterised by retention of memory and orientation in the presence of severely disordered emotion, thought and behaviour (Baldessarini, 1990). Idiopathic psychoses characterised mainly by chronically disordered thinking and emotional withdrawal, and often associated with paranoid delusions and auditory hallucinations are called schizophrenia. Those that are characterised by abnormal emotion or mood (disorders of affect with depression, dysphoria, elation or mania) are known as major affective or manic-depressive disorders. The affective disorders may be bipolar or non-bipolar. The bipolar illness includes periods of elation or excitement alternating with severe depression and autonomic changes, notably insomnia, anorexia, and altered daily rhythms of mood or activity (Pope and Lipinski, 1978).

To date, no single cause of schizophrenia has been identified, but several theories have emerged suggesting a number of possible causes of this mental disability. Psychological theories for instance, suggest that schizophrenics have impaired ability to handle the amount and speed of incoming perceptual stimuli and /or that some schizophrenics have a left hemisphere limbic dysfunction (Clare, 1991). A very popular social theory with poorly understood evidence, suggests that disturbances in family relationships or

communication may be responsible for schizophrenia (Clare, 1991). The biological hypotheses suggest that besides the genetic, social, psychological and environmental factors as well as brain damage, the dopaminergic pathways in the CNS have closely been correlated to schizophrenia (Clare, 1991). Pathways with cell bodies close to the substantia nigra project to the nucleus accumbens and olfactory tubercle, both components of the limbic system of the brain that regulate emotional behaviour. Dopaminergic pathways have been described with cell bodies in the same areas, projecting to parts of the frontal cingulate and internal cerebral cortex, phylogenetically older parts of the cerebral cortex functionally related to the limbic system (Gamaniel, 1984).

There are two major clues to the pathology of schizophrenia: that the psychosis induced by large doses of amphetamine closely resembles acute paranoid schizophrenia (Connell, 1958) and that range of psychotropic drugs (termed neuroleptics) are therapeutically effective in schizophrenia. These clues have led to the genesis of the DA hypothesis of schizophrenia. The theory states that, the symptoms of schizophrenia may be due to abnormal increase in central DA release and the effects of this increase are diminished by partial blockade of the receptor sites (Gamaniel, 1984).. Many behavioural effects of amphetamines are due to increased central dopamine (DA) release and most neuroleptic compounds are blockers of central DA receptors. Work with amphetamine showed that it does not only exacerbates schizophrenic symptoms (Janowsky *et al.,* 1973), but clinically, amphetamine psychoses is indistinguishable from schizophrenia (Connell, 1958). Amphetamine toxicity and psychoses has been suggested as an experimental

model for schizophrenia (Kety, 1959). The schizophreniform effects of amphetamine are better related to its dopaminergic activities rather than its noradrenergic activities (Synder *et al.,* 1978). Further more, L-dopa has been reported to exacerbate schizophrenic symptoms (Angrist *et al.,* 1973). Wise and Stein (1973) found that dopamine beta-hydroxylase activity is lowered in the brains of schizophrenics than in control subjects. Stevens *et al.* (1974) suggested a possible role for GABA in schizophrenia, from the behaviour displayed by the animals in their study. Recently David Jontsch provided evidence that support both dopamine and glutamate in hypotheses of schizophrenia (David, 1998).

Drugs with demonstrable efficacy in psychiatric disorders have been developed since the early 1950's. Many classes of drugs are effective in the symptomatic treatment of psychiatric disorders, but antipsychotic agents are those that are used primarily in the management of patients with psychotic or other serious psychiatric illnesses marked by agitation and impaired reasoning. They are most appropriately used in the therapy of schizophrenia, the manic phase of manic depressive illness and other acute idiopathic psychotic illnesses (Baldessarini, 1996). The antipsychotics together with antimanic and anti depressants drugs have effects on the cortical, limbic, hypothalamus and brain stem mechanisms that are fundamentally importance in the regulation of arousal, consciousness, affect, and autonomic functions. The physiological and pharmacological modification of these regions has important behavioural consequences and useful clinical effects regardless of the fundamental nature or cause of the mental disorder in question (Baldessarini, 1996). Contrary to a common misconception, the anti-psychotic drugs

exert beneficial effects in virtually all classes of psychotic illnesses and they are not selective to schizophrenia. However, these drugs have other clinically useful properties, including anti-emetic, anti-nausea, and antihistaminic effects and the ability to potentiate the actions of analgesics, sedatives and general anaesthesia (Baldessarini, 1990). Although the actions underlying their anti-psychotic and neurological effects remain uncertain, theories based on their ability to antagonise the action of dopamine as a neurotransmitter in the basal ganglia and limbic portions of the forebrain have become most prominent and are supported by a large body of data (Baldessarini, 1996). The ability to block DA receptors for instance, confers to phenothiazines both their anti-psychotic as well as their extra-pyramidal actions (VanRossum, 1966; Horn and Snyder, 1971). Further studies have also confirmed that anti-psychotic effects of neuroleptics might be mediated by the antagonism of dopaminergic neurotransmission in the limbic, mesocortical, and hypothalamic systems (Carlsson, 1978; Baldessarini and Tarsy, 1979). Interference with the transmitter function of dopamine in the mammalian forebrain might contribute to the neurological and possibly the anti-psychotic effects of neuroleptic drugs. This speculation is based on the observation that anti-psychotic drugs consistently increased the concentrations of the metabolites of dopamine but had variable effects on the metabolism of other neurotransmitters. The anti-psychotic drugs also increase the rate of conversion of the precursor amino acid tyrosine to dopamine and its metabolites increasing the rate of firing of putative dopamine-containing cells in the midbrain. These responses are eventually replaced by dismished activity ("depolarisation inactivation"), particularly in the extra pyramidal basal ganglia (Bunney *et al.,* 1987). Radio-ligand binding assays (using membrane fractions from mammalian caudate tissue as a source of

receptors and radio-labelled neuroleptic drugs or dopaminergic agonists as ligands) have been used to defined more precisely the mechanism of action of anti-psychotic agents (Creese *et al.,* 1978; Seeman 1980, Faedda *et al.,* 1989). The clinical potency of most anti-psychotic drugs correlate well with their relative potency in inhibiting the binding of these ligands to putative D2-dopaminergic sites *in vitro*. Thus, almost all the clinically effective anti-psychotic agents have characteristically high affinity for D2 sites (Creese *et al.,* 1978; Baldessarini, 1996; Bloom, 1996). Although some anti-psychotic agents bind avidly to D1-sites, those with relatively high affinity for D1-receptors also bind to and block D2-receptors (Peroutka and Synder, 1980; Faedda *et al.,* 1989). Other atypically anti-psychotic agents such as clozapine with weak antidopaminergic activity and little propensity to produce extra-pyramidal side effects also exist. They are potent alpha-adrenergic antagonists like other anti-psychotic agents (Peroutka and synder 1980; Cohen and Lipinski 1986a).

The effects of anti-psychotic agents on the hypothalamus or pituitary appear to involve dopaminergic pathways as well. Prominent among these is the ability of most anti-psychotic drugs to increase the secretion of prolactin in man. The effects of anti-psychotic agents on prolactin secretion is probably due to a blockade of the tubero-infundibular dopaminergic system that projects from the arcuate nucleus of hypothalamus to the median eminence by a direct antagonistic action at dopaminergic receptors localised on cells of the anterior pituitary (Baldessarini 1990). There is enough evidence to support the hypotheses that dopamine is the prolactin release-inhibiting hormone known to exist in the hypothalamus (Reichlin and Boyd 1978). The effects of

anti-psychotic drugs on the ANS are complex and unpredictable, since they have peripheral cholinergic blocking activity, α-adrenergic blocking actions, and adrenergic activity (Secondary to the block of neuronal re-uptake of amines). Antihistaminic as well as anti-tryptaminergic effects further complicate the picture (Godon 1974; Klein *et al.*, 1980; Baldessarini 1990).

In addition to other side effects, a variety of neurological syndromes, involving particularly the extra-pyramidal system, occur following the use of almost all anti-psychotic drugs. Varieties of neurological syndromes are particularly prominent during treatment with high potency neuroleptic agent (Tricyclic piperazine and butyrophenones). Four of these (acute dystonia, akathisia, parkinsonism, and the rare neuroleptic malignant syndrome) usually appear concomitantly with the administration of the drugs. Two (the rare perioral tremor and tardive dyskinesia) are late-appearing syndromes that occur following prolonged treatment for many months or years (Baldessarini *et al.*, 1980; Tarsy and Baldessarini, 1986). Risperidone is a novel antipsychotic with superiority over haloperidol in improving the symptoms of schizophrenia. New antipsychotic drugs (olanzepine and seatindole) possess several distintive pharmacological properties. e.g. $5HT_{2A}$ affinity greater than D_2 affinity, regional deplorization blockade action and antipsychotic properties .

1.3.2. Anti-anxiety Drugs

Anxiety is the feeling of fear, apprehension and dread. It is a cardinal symptom of many psychiatric disorders and is almost inevitable in many medical and surgical conditions.

Although it is a universal human emotion, closely allied with appropriate fear and often serving psychobiological adaptive purpose, it becomes a treatable medical condition when it is severe and interferes with normal daily functions. Anxiety disorders are among the most common of all CNS disorders afflicting millions, with the painful experience of tension and apprehension. Due to the prevalence of anxiety disorders, drugs that effectively reduce the cognitive and somatic manifestations of anxiety have been among the most commonly prescribed. The psychic experience of anxiety is described as fear, panic, apprehension, foreboding. These feelings are accompanied to variable extents by the somatic and physical components of anxiety which are consequences of sympathetic nervous system overactivity and many may be reproduced by injection of NA. Although some psychiatrists argue that most if not all anxiety is related to particular situations, there is evidence that anxiety neurosis and phobic anxiety are distinct groups. First, genetic influence appear to play a part in the etiology of anxiety neurosis but not phobic disorders. Secondly there seems to be a differential response to treatment in that anxiety neurosis respond well to drugs and poorly to psychological or behavioural treatment whereas the reverse is true for phobic states. (Baldessarini, 1996).

Based on behavioural and biochemical changes, and on the mechanism of action of some drugs that are effective in the treatment of anxiety, adrenergic and serotonergic systems in the CNS have been implicated in the pathogenesis of anxiety (Goman *et al.,* 1987; Coplan *et al.,* 1992). Most drugs used to treat anxiety are sedatives or at least have many properties in common with traditional sedatives. However the pharmacological treatment of anxiety disorders currently is based primarily on the use of BDZs anti-anxiety agents. e.g diazepam,

lorazepam, etc. Many other classes of drugs that act on the CNS e.g. barbiturates have been used, but their use for these conditions is now virtually obsolete.

Although several classes of drugs have been used to treat anxiety, BDZ's far outsell the others because of their greater safety margin than the other drugs, particularly barbiturates (Baldessarini, 1990). BDZs are the most commonly employed antianxiety agents for generalised anxiety disorder. Some BDZs (alprazolam, clonazepam and lorazepam) are effective in severe anxiety with strong autonomic overactivity (panic disorder). Potent BDZs (chlordiazepoxide, diazepam and lorazepam) are effective in panic disorder as well as in generalised anxiety disorder. Although commonly used for treatment of anxiety, these drugs share other therapeutic indications-notably sedation and induction of sleep, and as anticonvulsants. The following are amongst the benzodiazepines that are currently used in the treatment of anxiety. Chlordiazepoxide, diazepam, oxazepam, clonazepam prazepam, alprazolam. While the BDZ s continue to play an important role in anxiety disorders, there widespread use is on the wane. This is due, in no small part, to the concern about dependence and withdrawal phenomena associated with long term use.

1.3.3. Antidepressants

Antidepressant eg. TCAs, MAO inhibitors, lithium etc relieve depressive symptoms without inducing mental excitement or delirium (difference from psychotomimetic agents) or fit (difference from convulsants). They have an established role in the treatment of severe anxiety disorders, including panic agoraphobia syndrome, and in obsessive compulsive disorders. These agents are also employed in the management of post-traumatic stress

disorder, marked by anxiety, startle, painful recollection of the traumatic events, and disturbed sleep (American Psychiatric Association, 1994). Imipramine and phenelzine are the best-studied antidepressants in panic disorder, but other agents probably are effective, including the serotonin-reuptake inhibitors, which are now the agents of choice in obsessive-compulsive disorder (Baldessarini, 1996).

Depression itself is an emotional disorder that comprises of those feelings of mood which lie predominantly on the sad side of a happy-sad continum. When mild, it is a transient experience with no sequalae and is a normal, often appropriate emotion. However, depression can be so severe as to be regarded as an illness causing severe distress, disruption of life and potentially fatal. The major disorders of mood or affect include the syndromes of major depression and bipolar disorder (formerly manic depressive disorder). Major depression is one of the most common mental illnesses, and is distinguished from normal grief, sadness and disappointment and the dysphoria or demoralisation often associated with medical illness. Depression commonly includes disordered autonomic functioning (e.g. altered activity rhythms, sleep and appetite) and behavioural as well as persistent abnormalities of mood and increased risk of self-harm or suicide. Major depression is characterised by feelings of intense sadness and despair, mental slowing and loss of concentration, pessimistic worry, agitation, and self depreciation, insomnia or hypersomnia, anorexia and weight loss, decreased energy and libido, and disruption of normal circadian rhythms of activity, body temperature and many endocrine functions. Over 6% (About 100 million people) of the world's population experince major depression,

and upto 10-15% of individuals with the disorder display suicidal behaviour during their life time (Baldessarini, 1996).

There are etiologically two types of depression. Neurotic depression occurs as a result of stress (anxiety depression). Psychotic depression arises spontaneously in the mind (also known as endogenous depression). Generally, psychotic and medical illnesses may be associated with secondary mood disorder depression. Depresssion has been shown to be associated with life events e.g. bereavement, divorce, moving house etc and with certain social factors such as absence of close confiding relationship, lack of employment, loss of mother by death or separation before the age of 11 years. Most antidepressants exert important actions on the metabolism of monoamine neurotransmitters and their receptors. They increase synaptic monoamines in the brain but a coherent accounting of their mechanisms of action remains elusive. A few tentative generalizations have been made based on studies with animal models, and from the clinical and behavioral effects of antidepressant drugs, that inhibition of serotonin and noradrenaline uptake may provide antidepressant effects, while the same may not be said of dopamine. The 5-HT system and the catecholamine neurotransmitter systems have been implicated in depressive illness (Baldessarini, 1996).

Recently, a series of innovative antidepressants have emerged (e.g. fluoxetine). They are mostly characterized as inhibitors of the neuronal serotonin reuptake with little effect on the noradrenergic system. Others, like trazodone, nefazodone and bupropion, have less well-defined neuropharmacology and can be considered "atypical". Some like iprindole and

mianserin have little effect on reuptake systems but are clinically effective antidepressants (Baldessarini, 1996). The relative safety and tolerability of the newer agents has led to their rapid acceptance as the most commonly prescribed antidepressants.

To a great extent, the development of novel antidepressants is limited by our inability to predict antidepressant activity in preclinical tests using animal models. Laboratory tests have been dependent on models demonstrating evidence of protentiation of the biochemical, physiological, or behavioral actions of cerebral monoamines. Indeed, it is difficult for a novel compound to be considered as a potential antidepressant if it lacks such effects, yet truly novel agents that might alleviate depression in human beings might act by unanticipated mechanisms not involving the functioning of central monoamines.

1.3.3.1. Tricyclic Antidepressants (TCAs)

The tricyclic antidepressants (TCAs) are the most widely used agents in depressive illnesses. Provided that adequate doses are used for a sufficient period of time, they are all apparently similar in efficacy for depression (Simpson *et al.*, 1976; Stewart *et al.*, 1980,). The onset of action of the TCAs is often delayed for up to 2 to 3 weeks and they all require several weeks to exert clinically important antidepressant actions (Baldessarini , 1990). TCAs have been used occasionally as hypnotics because of their sedative properties and this may be useful in the initial therapy of a depressed patient who is not sleeping well (Kupfer *et al.*, 1981).

Tricyclic antidepressants potentiate the actions of biogenic amines by blocking their major means of physiological inactivation, which involves transport or reuptake into nerve terminals (Hoffman and Lefkowitz, 1996). However there are compounds which are equivalent in antidepressant action to tricyclics but do not inhibit reuptake thus antidepressant action and reuptake inhibition do not seem to be inter-related. e.g. iprindole and mianserin (Baldessarini, 1996). Imipramine blocks the reuptake of norepinephrine. Imipramine and its congeners with tertiary-amine side chain also have effects on the reuptake of serotonin though they have little effect on the reuptake of dopamine. Clomipramine, has marked effects on serotonin uptake, desipramine and nortriptylline, are potent and highly selective inhibitors of norepinephrine reuptake; fluoxetine and other inhibitors of serotonin transport have relatively selective effects on reuptake of serotonin, with relatively limited direct action at other sites, including cholinergic and other transmitter receptors (Koe, 1990; Beasley *et al.,* 1992).

Other interactions of tricyclic antidepressants include appreciable antimuscarinic and antihistaminic activity. For example, amitriptyline and imipramine have relatively high affinity at muscarinic, α_1-adrenergic, and both H_1 and H_2 histamine receptors (Cusack *et al.,* 1994). The activities of the TCA's on the ANS are believed to result from inhibition of noradenaline transport into the adrenergic nerve terminals and also from antagonism of muscarinic, cholinergic and α1-adrenergic responses to the autonomic neurotransmitters (Baldessarini, 1996). The blurred vision, dry mouth, constipation, and urinary retention produced by therapeutic doses of TCAs are manifestations of anticholinergic actions (Blackwell *et al.,* 1978). Furthermore, TCAs decrease the SMA, impair both acquisition

and performance of conditioned avoidance responses, and are also capable of stimulating a variety of behavioural patterns (such as potentiation of the effects of amphetamine, augmentation of operant behaviours etc). These seem to be closely related to the potentiation of amine-mediated (particularly noradrenergic) synaptic transmission in the CNS (Lowe *et al.*, 1978).

1.3.3.2. Monoamine Oxidase Inhibitors (MAOIs)

Zeller (1952) demonstrated that iproniazid and isoniazid inhibited the enzyme MAO which is responsible for the degradation of the brain monoamines. It was noted at the same time that some patients being treated for tuberculosis with these drugs became euphoric. These observations therefore lead to the hypothesis regarding the biochemical mechanisms of mood disorders, that: (1) depletion of monoamines (e.g by reserpine) produced depression and (2) elevation of brain concentrations of monoamines (eg by MAO inhibitors) produced mood elevation.

The MAOIs comprise of a chemically heterogeneous group of drugs that have in common the ability to block oxidative deamination of naturally occurring monoamines (Murphy *et al.*, 1987). The MAOIs sometimes have severe and often unpredictable interactions with many drugs and food containing amines making their medical use difficult and potentially hazardous. Although MAOIs are probably as effective as TCAs in the treatment of major depression, their use in psychiatry has become limited as the TCA's and newer atypical antidepressants have dominated the treatment of depression and similar conditions (Murphy *et al.*, 1987).

MAO inhibitors exert their effects mainly on organ systems influenced by sympathomimetic amines and serotonin. These agents inhibit not only MAO but other enzymes as well, and they interfere with the hepatic metabolism of many drugs. The capacity of MAO inhibitors to act as antidepressants has been assumed most often to reflect the increased availability of one or more monoamines in the CNS or sympathetic nervous system, although this assumption has been difficult to prove. It has been generally assumed that these compounds achieve their therapeutic effect by increasing the function of the monoamines since the major degradative enzyme of these neurotransmitters is inhibited. Administration of MAOIs to patients often does not achieve a high degree of enzyme inhibition, as measured by the activity present in human post mortem brains of people who have been taking MAOIs until death (Murphy *et al.*, 1987). Furthermore, the lack of relationship between the onset of enzyme inhibition (in the platelets for example which occur promptly) and clinical response to the drugs (which takes 2-3wks) is confusing and may indicate that enzyme inhibition initiates a series of other changes which are finally responsible for the therapeutic effect (Baldessarini, 1996). MAOIs are often employed when ECT is inappropriate or refused and the use of TCAs give unsatisfactory result. It has been suggested, with some scientific support, that whereas severe depression may not be the primary indication for these agents, certain neurotic illnesses with depressive, anxiety and phobic features may respond favorably to them (Robinson *et al.*, 1978; Klein *et al.*, 1980; Baldessarini, 1985). The MAOIs suppress REM sleep and they correct the sleep disorders accompanying depression. They either prolong or shorten the sleeping time. Even at elevated concentrations of dopamine, noradrenaline and 5HT in the CNS, MAOIs produce minor or no changes in the behaviour of experimental animals. However, when combined with

other drugs, marked effects may be observed. The actions of many other CNS depressants and stimulants may be augmented, and hexobarbital sleeping time may be prolonged (Baldessarini, 1990).

1.3.4. Antimanic Agents

Mania is a phase of manic - depressive psychoses in which the prevailing mood is that of an undue elation and a pronounced psychomotor overactivity and often pathological excitement. It is characterised by excessive excitement, typically tinged with dysphoria or marked by irritability, severe insomnia, hyperactivity, uncontrollable speech and activity, and impaired judgement.

In some patients, episodes of depression alternate with episodes of mania. The clinical features are in some ways the reverse of those seen in depression, mainly speeded up thoughts and talk, many new ideas and sense of well being. Patients with recurrent mania usually show symptoms and signs of depression at some stages. It is possible to experience manic symptoms without ever getting depressed, but this is uncommon and patients with recurrent mania usually show symptoms and signs of depression at some stages. As with the diagnosis of depression, the cardinal feature of mania is altered mood, in this case a hightening of mood to cheerfulness, elation and euphoria. The mood change is more labile than that seen in depression and while some consistent diurnal variations may be observed, more rapid minute to minute changes are common. Other mood changes such as iritability and hostility, general disinhibition, impaired judgement, uncontrolled speech and activities are common. Overactive behaviour with constant movement, which would in other

circumstances be completely exhausting, is invariable. Overactive thoughts are evident in both the spoken and written words. Flight of ideas, rapid change in the subject of thought together with a general pressure of talk, make any effective dialogue difficult. There is certainly no evidence for either the 5HT or catecholamine systems being changed in 'opposite' direction in depression and mania. Biochemically these illnesses show distinct similarities. Several reports have shown that CSF 5-HIAA concentration is increased. In general the initial treatment of mania is the use of a major tranquilizer such as haloperidol. The antimanic action of major tranquilizers is presumably through their dopamine antogonist actions. This has the effect of making the patient "manageable". Lithium (as salt) also has an antimanic action but usually takes over a week to work and is thus not usually the drug of choice on admission to hospital. While lithium does not act rapidly as an antimanic drug its action as a prophyllactic drug to prvent further manic episodes is proven. Whether it does so by preventing the illness or treating the underlying illness when it occurs has not been ascertain.

Unlike other psychotropic agents, the therapeutic concentrations of lithium have no discernable psychotropic effects (such as sedative, depressant or euphoriant properties) in normal individuals (Schou, 1969). The mechanism of action of lithium as a mood - stabilising agent is not well understood but effects on biological membranes and synaptic neurotransmission are suspected (Baldessarini, 1996). In animal brain tissue for instance, low concentration of lithium inhibits the depolarisation provoked and alpha 2- dependent release of noradrenaline and dopamine but not 5HT from nerve terminals (Baldessarini and Vogt, 1988). Lithium may enhance the release of 5HT especially in the

hippocampus (Treiser *et al.*, 1981) It may also slightly alter reuptake and presynaptic storage of catecholamines in directions consistent with increased inactivation of the amines. The effects of Li+ on the distribution of Na^{+}, Ca^{++} and Mg^{++} as well as glucose metabolism have been suggested to contribute to the antimanic or mood stabilising effects of the ion, but non of these hypotheses has been substantiated (Baldessarini, 1990). Another hypotheses are that, treatment with Li^{+} could selectively modulate the function of hyperactive neurons that contribute to the manic state (Berridge *et al.*, 1982; Worley *et al.*, 1988; Casebolt and Jope 1989).

Mania and its mild form (hypomania) are treated with anti-psychotic drugs or lithium salts in short term, and lithium salt or certain anticonvulsant for longer terms prevention of recurrences. Benzodiazepines such as clonazepam or lorazepam are sometimes used as sedatives early in acute mania, but they do not have demonstrable efficacy in long-term prevention of manic-depressive recurrences (Cohen and Lipinski, 1986b; Rosenbaum, 1987). Other agents with limited assessment in the treatment of mania include various antihypertensive agents, including clonidine and Ca^{++} channel blockers such as verapamil, their effects however appear to be weak, inconsistent, or temporary (Cohen and Lipinski, 1986b).

1.3.5. Hypnotics and Sedatives

The sedative hypnotic drugs such as benzodiazepines, barbiturates, paraldehyde, chloral hydrate etc depress the CNS in a relatively non-selective and dose-dependent manner producing progressively calming or drowsiness (sedation), sleep (hypnosis),

unconsciousness, coma, surgical anaesthesia and fatal depression of respiration and cardiovascular regulations (Theodore, 1990). A sedative drug decreases activity, moderates excitement and calms the recipient, whereas a hypnotic drug produces drowsiness and facilitates the onset and maintenance of sleep state that resembles natural sleep in the EEG characteristic and from which the recipient can be aroused easily. Hypnotic sedatives are drugs which selectively induce sleep or calmness in the patients. The hypnotic sedative drugs have pharmacological properties that are quite similar to those of general anaesthetics. When large doses are used, as in suicide attempt or when a barbiturate such as thiopental is used to induce general anaesthesia (GA), the difference between a sedative-hypnotic and general anaesthetic disappears. These drugs act via different mechanisms to induce depressant action on the central nervous system. However behavioral and electrophysiological studies supports the predominant view that most, if not all, the actions of sedative hypnotic agents occur as a result of neural inhibition that is mediated by Gamma-amino butyric acid (GABA).

1.3.5.1. Benzodiazepines

As a result of the detection and characterisation of specific binding sites for benzodiazepines, a substantial body of biochemical evidence has accumulated that suggests a close molecular association between sites of action for GABA and the benzodiazepines (Dubnick *et al.,* 1983, Polc, 1988). Various categories of evidence have been brought together by the discovery that certain congeners of the benzodiazepines are potent and selective inhibitors of both their biological effects and their binding to putative sites of action (e.g. flumazenil) (Theodore, 1990). Studies have shown a

substantial enhancement of GABA-induced chloride currents in cultured neurons using either diazepam or clonazepam (Macdonald and Mclean, 1986). These effects appear to result from an increase in the frequency of burst of openings of chloride channels induced by sub-maximal amounts of GABA (Twyman *et al.*, 1989).

It is worth noting that benzodiazepines produce no effects on chloride conductance in the absence of GABA (Theodore, 1990).

1.3.5.2. Barbiturates

The barbiturates can produce all degrees of CNS depression, ranging from mild sedation to general anaesthesia. However, in some individuals depending on the circumstances (such as in the presence of pain), barbiturates can cause overt excitation. This indicates that the effects of barbiturates may not be entirely mediated by GABA but that they may exert several distinct effects on excitatory and inhibitory synaptic transmission (Theodore, 1990). They potentiate GABA induced increases in chloride conductance and reduce glutamate-induced depolarisation (Macdonald and Mclean, 1982). The capacity of the barbiturates to facilitate GABA-ergic inhibition resembles some of the actions of the benzodiazepines. However, promotion of GABA induced chloride currents by barbiturates appears to result from prolongation of periods during which bursts of channel openings occur, rather than by increasing the frequency of bursts of channel openings (Twyman *et al.*, 1989). Barbiturates do not displace benzodiazepines from their binding sites, but enhance such binding and the binding of GABA. These effects are almost completely dependent upon the presence of chloride or other anions

that are known to permeate through chloride channels, and they are completely antagonised by picrotoxin (Richter and Holman, 1982).

Barbiturates selectively depress transmission in autonomic ganglia and reduce nicotinic excitation by choline esters. These effects may account at least in part, for the fall in blood pressure produced by severe barbiturate intoxication. At the skeletal neuromuscular junctions, the blocking effects of both tubocurarine and decamethonium are enhanced during barbiturate anesthesia (Theodore, 1990).

1.3.5.3. Aliphatic Alcohols

Alcohols are primary and continuous CNS depressants. Other agents that depress the function of CNS augment the effects of alcohol. The effects are very much enhanced in individuals who have taken sedatives, hypnotics, anti-convulsants, anti-depressants, anxiolytics, and analgesics such as opioids.

The layman view of alcoholic drinks is that they are stimulants. The apparent stimulation results from the depression of inhibitory control mechanisms in the brain. Chronic excessive ingestion of alcohol is directly associated with serious neurological and mental disorders (e.g. brain damage, memory loss, sleep disturbances and psychosis). Acute and chronic administration of alcohol produces a variety of effects on sleep (Mendelson, 1979). Since Chin and Goldstein (1981) reported the membrane fluidizing effects of ethanol, a number of investigators have shown a correlation between the degree of intoxication and the extent of ethanol-induced disordering of membranes (Wood and

Schroeder, 1988). Attention has also been focused on the capacity of ethanol to augment GABA-mediated synaptic inhibition as well as fluxes of chloride (Ticku and Kulkarni, 1988). A specific antagonist at the GABA-ergic receptors (bicuculine) inhibits these sedative - ataxic actions of alcohol. At higher concentrations, aliphatic alcohols increase chloride permeability in the absence of GABA. These actions are not well correlated with fluidizing effects on the bulk membrane (Huidobro-Toro *et al.,* 1988). Experiments in animals have shown a wide variety of effects of alcohols on biogenic amines in the CNS. The most consistent of these is the increased turnover of noradrenaline while the concentration of ethanol is rising following acute administration, or during it long term administration (Pohorecky and Brick, 1988). The fact that naloxone can prevent or reverse such effects, as well as many of the manifestations of alcohol intoxication, has invited numerous speculations on the possible relationships between the actions of opioids and alcohols (Theodore, 1990).

1.3.6. Anticonvulsant Agents

Convulsion is an involuntary contraction of the muscles resulting from abnormal cerebral stimulation from many causes with or without loss of consciousness. Epilepsy is a collective term used to describe a chronic brain syndrome of various aetiology, characterised by recurrent seizures (convulsion) due to excessive discharges of cerebral neurons, and associated with a variety of clinical and laboratory manifestations. The clinical symptoms are disturbances of consciousness, movement and sensation. In the laboratory, the electroencephalography (EEG) shows hypersynchronisation (simultaneous occurrence) of electrical activity of the brain (Theodore and Leonard,

1990). Anticonvulsants are compounds which have potential values in the treatment of epilepsy. The term antiepileptic agent is often restricted to those compounds which have been established to be effective in clinical epilepsies. Although, the pathophysiology of epilepsy is poorly understood, the complex interaction of multiple causative factors, such as macroscopic lesions of the brain has been implicated. At the microscopic level, glial proliferation and loss of neurons, together with evidence for loss of inhibitory synaptic elements containing GABA have been reported in epileptic patients (Ribak, 1986). However, it is not clear whether such changes preceed the development of epileptic foci or whether they might represent the consequences of seizures and simply contribute to the spread of seizure discharges.

Several drugs have been discovered which are effective in the management of epilepsy (e.g. phenobarbitone, paraldehyde, clonazepam, carbamazepine, diazepam, folic acid, sodium valproate, diphenylhydantoin etc). Anticonvulsant agents interfere with seizures in two general ways, (a) prevention or reduction of excessive discharges of pathologically altered neurons at seizure foci and (b) reducing the spread of excitation from seizure foci thereby preventing detonation and disruption of function of normal aggregates of neurons (Macdonald and Kelly, 1993). Anticonvulsant agents modify the ability of the brain to respond to various seizure-evoking stimuli via a number of mechanisms which include; increase in fore brain GABA (or increase in efficiency of GABA-ergic synapses) resulting to increased chloride ion conductance and hyperpolarisation. Other mechanisms include membrane stabilisation and prevention of post-tetanic potentiation (responsible for increased activity of a junction resulting to

enhanced pre-synaptic release of transmitter together with modulation of the Na^+-K^+-activated ATPase (vital in maintaining transmembrane ionic gradient). Phenytoin (a prototype of diphenylhydantoin) decreases resting fluxes of Na^+ as well as Na^+ currents that flow during action potentials or chemically induced depolarisation, probably by the inhibition of voltage sensitive Na^+ channels which is dependent on both voltage and frequency (Jones and Wimbish, 1985). As a result, phenytoin suppresses episodes of repetitive neuronal firing that are induced by passage of intracellular currents. Phenytoin delays the activation of outward K^+ currents during action potentials in nerves, leading to an increased refractory period, and can also reduce the size and duration of Ca^{++} dependent action potentials in cultured neurons (Mclean and Macdonald, 1983; Yari *et al.*, 1986).

Carbamazepine and phenytoin appear to have virtually identical actions on Na^+ channels (Willow and Catterall, 1982, Willow *et al.*, 1985). Current hypothesis on the mechanism of action of valproate has centered on potential interaction with voltage sensitive Na^+ channels (Macdonald, 1988) and on possible enhancement of GABA accumulation (Loscher, 1985). Although valproate has no effects on responses to GABA, it does increase the amount of GABA that can be recovered from brain after the drug is administered to animals.

The anticonvulsant actions of the benzodiazepines as well as other effects occur at non sedating doses and result in large part from their ability to enhance GABA-induced increases in the conductance of chloride ion (Mennini *et at.*, 1987). Diazepam and other

active benzodiazepines augment the inhibitory effects produced by stimulating various GABA-induced changes in membrane potentials. Extensive biochemical evidence suggests a close molecular association between specific binding sites for benzodiazepines and GABA regulated chloride channels (Twyman *et al.,* 1989). There may be other mechanisms by which benzodiazepines reduce the excitability of neurons. These include enhancement of Ca^{++} dependent K^{+} conductance and of adenosine accumulation, neither of which requires GABA.

The ability of phenobarbitone, at therapeutic concentrations, to reduce the excitatory effects of glutamate and augment the inhibitory effects of GABA may be important to its anticonvulsant activity. Macdonald and Mclean (1986) proposed that the low potency of phenobarbitone (relative to that of pentobarbitone) both in producing GABA-like increase in the conductance of chloride and reducing Ca^{++} dependent release of neurotransmitters may account for the relatively selective effects of anticonvulsant barbiturates. However, pentobarbitone is much less potent than phenobarbitone in antagonising seizures induced by pentylenetetrazole (Woodbury and Pippenger, 1982).

1.3.7. Drugs used in the Treatment of Parkinsonism

Parkinsonism (Paralysis agitans) is associated with lesions in the substantia nigra and globus pallidus that result in increase but improper modulation of motor activity by the extrapyramidal system. The clinical syndrome comprises of four cardinal features namely bradykinesia (slowness and poverty of movement), muscular rigidity (increase in the resistance of the muscles to passive movement), resting tremor (which usually abates

during voluntary movement), and abnormalities of posture and gait. The incidence of Parkinson's disease increases with age. It afflicts approximately 1% of all adults over the age of 65 world wide, and usually becomes manifested after the age of 55 (Martilla, 1983). Despite advances in the understanding of the pathophysiology and the treatment of Parkinson's disease, its cause remains unknown. Although, familial cases have been documented, genetic factors do not seem to play any important role in most cases of Parkinson's disease (Ward *et al.,* 1983).

Over the last four decades, there has been a major development in the accumulation of evidence that, there is a marked deficiency in the dopaminergic innervation of the basal ganglia of patients with Parkinson's disease, owing to degeneration of neurons in the substantia nigra (Ehringer and Horny Kiewicz, 1960). The pigmented neurons of the substantia nigra utilize dopamine as their neurotransmitter. 80-90% depletion of this catechole amine has been shown to underlie all of the major motor manifestations of parkinsonism. The restoration of dopaminergic transmission restores motor function in parkinsonism, and forms the central strategy in virtually all current drug regimens for treatment of the disease (Jesse and Leonard, 1990). The therapeutic implications of this discovery were pursued and attempts were made to replenish brain dopamine by giving patients its immediate precursor-levodopa (L-dopa) because dopamine itself does not readily cross the blood-brain barrier. A hypothesis emerged from the results of these studies, that acetylcholine and dopamine act as physiological antagonists to each other in the CNS just as in the peripheral nervous system (Gamaniel, 1984).

Anti-psychotic drugs such as phenothiazines and butyrophenones have the capacity to prevent the action of the neurotransmitter dopamine in the basal ganglia, by blocking postsynaptic receptors of dopamine and cause extrapyramidal symptoms that resemble parkinsonism, especially in older patients. Reserpine on the other hand, produces a parkinsonism-like syndrome by depleting dopamine available for release by the presynaptic neuron.

Many investigators have documented the striking effect of L-dopa in relieving parkinsonian symptoms when it is administered in large doses (Cotzias *et al.,* 1969). Essentially all signs and symptoms parkinsonism except dementia and postural inability can respond to the administration of levodopa (Cedarbaum and McDowell, 1986). The neostriatum (caudate nucleus and putamen) normally contains balanced inhibitory dopaminergic and excitatory cholinergic components (Duvoisin, 1967). Although cholinergic neurons are not damaged in Parkinson's disease, the decrease in dopaminergic activity results in a relative excess of cholinergic influence. Thus a historically older strategy for the treatment of parkinsonism is to block cholinergic activity in an attempt to restore the balance of dopaminergic and cholinergic activities in the striatum. However, dopaminergic agonists (such as l-dopa, apomorphine, amantadine, etc), and cholinergic antagonists (such as benztropine, trihexyphenidyl etc) are often combined effectively.

1.3. 8. Analgesics

Analgesics are drugs used to relieve pain without loss of consciousness or sense of touch. The narcotic analgesics relieve severe pains, while the non-narcotic analgesics are used to relieve mild pains e.g. headache, joint, muscle, rheumatic pains and pains generally arising from structures rather than internal organs. The unique features of non-narcotic analgesics are the anti-rheumatic, antipyretic, and anti-inflammatory properties. The narcotic analgesics are drugs of addiction and their use is associated with the development of tolerance, physical or psychological dependence, while the non narcotic analgesics are not drugs of addiction and their use is not associated with psychological or physical dependence, and they are freely available.

1.3.8.1. Narcotic Analgesics

The narcotic (morphine-like) analgesics are employed primarily as analgesics, but they have many other pharmacological effects. They produce analgesia, drowsiness, changes in mood, and mental clouding. Radio-ligand binding assays in the brain and other organs suggest the existence of three major categories of opioid receptors in the CNS, designated M (mu), K (kappa) and D (delta) , and two subtypes of each category have been identified tentatively (Jerome and Williams, 1990). The narcotic analgesics interact with these groups of receptors, and they share some properties with endogenous opioid neuropeptides such as enkephalins, endorphins and dynorphins (Jerome and Williams, 1990). Martin (1983) reported that a given opioid drug might interact with all the three types of these receptors and act as agonist, partial agonist, or an antagonist at each. Although the location of the receptors vary, they are often found on presynaptic nerve

terminals, where their action results in decreased release of excitatory neurotransmitter and they all appear to be coupled to guanine binding regulatory protein (Jerome and Williams, 1990). The narcotic analgesics produce their major effects on the CNS and the bowel by acting as agonists to opioid receptors (M,K, and D). The effects produced include analgesia, drowsiness, changing in mood, respiratory depression, decreased gastrointestinal motility, nausea, vomiting, and alterations of the endocrine and autonomic nervous systems (Martin and sloan, 1977; Duggan and North, 1983; Martin, 1983). Analgesia is due to actions of the opioid analgesics at several sites within the CNS. The various mechanisms involved include the inhibition of the release of neurotransmitter, including substance P. Both D and K agonists appear to act similarly; they slightly suppress thermal stimuli and their maximal effects on visceral pain are distinctly lower (Lewis *et al.*, 1987).

The mechanism by which narcotic analgesics produce euphoria, tranquillity, and other alterations of mood is not clear, but the micro injection of M-opioids into the ventral tegmentum activates dopaminergic neurons that project to the nucleus accumbens. This pathway is believed to be important in the reinforcing effects of opioids and opioid-induced euphoria. The administration of dopaminergic antagonists on the other hand, does not prevent the reinforcing effects of narcotic analgesics, suggesting that some non-dopaminergic mechanisms may also be involved. The activation of D-receptors may also produce reinforcing effects, while M and K agonists inhibit the firing of dopamine containing cells in the substantia nigra and inhibit dopamine release from cortical and striatal neurons, thus they produce dysphoric effects rather than euphoria (Walker *et al.*,

1987; Werling *et al.*, 1998). Opioids and endogenous peptides cause catalepsy circling and stereotypical behaviour in rats and other animals. These effects are related to their actions at opioid receptors in the subsantia nigra and striatum, which involve the interactions with both dopaminergic and GABA ergic neurons. The narcotic analgesics can alter the equilibrium point of hypothalamic heat-regulatory mechanisms such that body temperature usually falls slightly; chronic high dosage may increase body temperature (Martin, 1983).

1.3.8.2. Non-narcotic Analgesic

Non-narcotic analgesics are a heterogeneous group of chemically related compounds with anti- inflammatory, analgesic, and antipyretic properties. They include salicylates, aniline derivatives, pyrozolone and indole derivatives etc. Their therapeutic activity appears to depend to a large extent upon inhibition of a defined biochemical pathway responsible for the biosynthesis of the prostaglandins and related autacoids (Insel, 1996). There is evidence that prostaglandins participate in the pathogenesis of inflammation and fever (Higgs *et al.,* 1974), During the complex inflammatory response, chemical mediators such as histamine, 5-HT, various chemostatic factors, bradykinin, lenkotrienes, and postaglandins are liberated locally (Insel, 1996). Prostaglandins intensify the action of chemical mediators of pain and inflammation and non-narcotics act by inhibiting the synthesis of the prostaglandins. The analgesic properties of non-narcotic analgesics are by direct central hypothalamus and peripheral (pain receptors) mechanisms. Peripherally, they depress the sensitivity of the pain receptors to chemical (histamine, 5HT, bradykinin) and mechanical stimuli (Konttinen *et al.,* 1994). They do not affect

receptors of sensory nerves subserving sensation other than pain e.g. touch. The antipyretic action of non-narcotic analgesics are believed to be operated at the hypothalamic temperature-regulating center. They reset the central thermostat to normal and reduce body temperature by causing peripheral vasodilatation (Saper and Breder, 1994).

1.3.9. Analeptics

Analeptics are drugs that produce CNS stimulation as their primary action. The drugs are capable of stimulating the nerve cells of the midbrain and medulla at normal therapeutic doses. They are generally used to revive failing respiration due to depressant action of drugs including barbiturates, alcohols etc. The central nervous system stimulants include strychnine, picrotoxin, pentylenetetrazol, miscellaneous agents (such as Doxapram, Nikethamide, methylphenidate), and methylxanthine (theophylline, Caffeine, and theobromine). Although a large number of other natural and synthetic substances can produce stimulation of the CNS, only a few have been used therapeutically. Some drugs exhibit prominent central stimulation at toxic levels, and others produce mild stimulation as a side effect. Strychnine interferes with the post-synaptic inhibition that is mediated by glycine. Glycine is an important inhibitory transmitter to motor neurons and interneurons in the spinal cord, and strychnine acts as a selective, competitive antagonist to block the inhibitory effects of glycine at all glycine receptors (Kuno and Weakly, 1972). The specificity of the binding of strychnine to glycine receptors has been used to demonstrate their dense localization in the gray matter of the spinal cord, brain stem, and thalamus by autoradiographic techniques (Zarbin *et al.*, 1981). Competitive receptor-

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binding studies indicate that both strychnine and glycine interact with the same receptor complex, although possibly at different sites (Johnston, 1978). Strychnine sensitive postsynaptic inhibition in higher centers of the CNS is also mediated by glycine.

Tetanus toxin also blocks postsynaptic inhibition, but it acts by preventing the release of glycine from inhibitory interneurons (Curtis, 1969). Penthylenetetrazole, picrotoxin and bicuculine produce convulsions by blocking the inhibitory pathways mediated by the predominant inhibitory transmitters gamma-amino butyric acid (GABA), at all levels of the CNS (Johnston, 1978; scholfield, 1982). In addition, pentylenetetrazol appears to interact with binding sites for picrotoxin and to block the enhanced binding of GABA and benzodiazepines that is produced by hypnotic barbiturates (Olsen, 1982). It is now a common knowledge that GABA receptors are coupled to ionophores that permit the influx of chloride with resultant hyperpolarisation of neuronal membranes. Picrotoxin antagonises the effects of GABA, perhaps by interacting with sites closely associated with the ionophore. Bicuculine on the other hand, interacts directly with the GABA receptors and is therefore a true antagonist (Johnston, 1978; Olsen, 1981).

1.3.10. CNS Disorders and Medicinal Plants

The importance of herbs and other flora as healing agents have been recognised for thousands of years by contributions of the primitive men all over the world. Some plants are used to relieve symptoms of discomfort or sickness, a few others as nourishment, while a number of these plants are lethal and some elevate mood (Thomson, 1978). Man by gradual processes of trial and error, was able to sort out these plants according to their

various uses, and the knowledge handed down from one generation to another. Today, a number of plants are used as medicines, and the plant kingdom and the forest are often referred to as the sleeping giant of drug development and God's own pharmacy respectively (Treben, 1986; Verpoorte *et al.,* 1987).

Quite a number of medicinal plants discovered by traditional societies are proving to be important sources of potential therapeutic agents. e.g. quinine (antimalarial agent) from *Cinchona* bark, reserpine (tranquilizer) from *Rauwolfia serpentina*, vincristine and vinblastine alkaloids (antileukaemic agents) from *Catharantus rosea*, digoxin and digitoxin (cardiotonic activity) from *Digitalis purpurea*, zingeberone (antihelmintic) from Zingiber officinalis, bouvardine from *Bouvardin ternifolia* and sinocaculine from *Corculus tribolus* both used as anticancer agents etc (Hardman, 1991).

The medicinal property of any plant may be due to the presence of a variety of chemical substances such as phenolic compounds; terpenes, alkaloids, glycosides, anthraquinones, saponins and a host of others referred to as primary and secondary metabolites (Hardman, 1991). Many of these compounds have prominent effects in the animal system and some possess important therapeutic properties, which can be and have been utilized in the treatment and cure of human and other animal diseases. A considerable number of plants are still being investigated for possible therapeutic applications. The plants *Portulaca olaracea*, *Jatropha elliptica* and *Gossypol* for instance were tested and found to have skeletal muscle relaxant, cardiac inhibitory and bronchodilatory effects respectively (Okwuasaba *et al.,* 1987; Joao *et al.,* 1987; Caroline *et al.,* 1987). Similarly,

Amos *et al.* (1998), reported that the aqueous extract of *Pavetta crassipes* leaves produced a concentration-dependent inhibition of the spontaneous motility and elevated tone of gastrointestinal and uterine smooth muscle preparations isolated from rabbit, quinea pig and rats. The inhibitory effects of the extract were not affected by pretreatment with propranolol or yohimbine, but were completely blocked by verapamil pretreatment, suggesting the presence of biologically active substances whose action might be mediated through calcium channels.

One of the major areas in which traditional medicine enjoys high patronage is in central nervous system disorders, and the use of medicinal plants to modify mood and feelings. Psychotropic plants are botanically diverse but they produce similar effects on the human CNS. Various cultures frequently maintain within their collection of traditional medicines, substances valued as tonics or stimulants, and they represent a potentially valuable untapped source of active psychoactive drugs for treating mental diseases such as depression. *Rauwolfia Vomitoria* and other *Rauwolfia* species are components of herbal preparations used to treat mentally disturbed patients. Old records mentioned the ancient names of sapagadha and chandra, the latter meaning moon and referring to the use of *Rauwolfia serpentina* root in moon disease i.e. Lunacy, (Taylor, 1965). Some traditional medicinal plants used in mental illness include *Piper guineense* seeds (*Piperaceas cymbopogon*), *Citratus graminae*, and lemon grass, *Lonchocarpus cyaneseus* (Papillionaceae). The west Africa black pepper or Ashanti have been shown to contain several amide alkaloids as well as sterols or ligands, and some of these constituents have demonstrated, anticonvulsant, antihypertensive, sedative, tranquilizing

and insecticidal properties (Addac-mensah *et al.*, 1977). Sokomba *et al.* (1986) demonstrated that the alkaloidal extracts of the leaves of *Synclisia scabrida* Miers possessed anti-psychotic and antimicrobial effects, which partly justify the use of the plant by traditional healers for the treatment of various abdominal and mental ailments. Wambebe *et al.* (1997) further confirmed that cycleanine, an alkaloidal extractive from the root bark of *Synclisia scabrida* may play a sedative role in the use of the crude extracts of the plant for psychotic conditions in traditional medicine. These workers also reported that, the *In vitro* studies using isolated rat uterus showed that clycleanine evoked dose dependent contractions that were resistant to atropine but blocked by salbutamol. Ming-chin Lu (1998) reported that the crude extract of *Cistancle deserticola* could prolong the hexobarbital-induced sleeping time and reduce spontaneous motor activity, including horizontal activity, ambulatory time and total distance, in rats suggesting that the extracts possessed sedative effects.

Majority of the plants used in traditional medicine lack scientific verification. Many medicinal plants are used in various ways because of their activities on the CNS. However, only limited efforts have been made to evaluate the potentials of such plants for their use in modern medicine or to scientifically justify their traditional use in the treatment of CNS disorders. Some of these plants hold great promise for psychotropic application.

1.3.11. Objectives of the Study

Traditional medicine enjoys a very wide acceptability especially among the people of developing countries and it blends readily into the socio-cultural life of the people in whose culture it is deeply rooted. Consequently a number of people do patronise traditional healers. A lot of interest is being generated towards the use of herbs, particularly those with demonstrable values and safety whether fully evaluated or not. The increasing interest in the medicinal properties of plants has a number of environmental and health implications. Therefore a proper pharmacological evaluation of such plants is necessary in order to properly define their true activities so as to ensure correct use and application. This approach will stimulate substainable use of the plants, since the people will be interested in protecting those that they may consider valuable to them. *Ficus platyphylla* (moraceae) is a deciduous tree plant commonly found in the west coast of Africa in the savannah region. The plant has been used for various purposes in this region, including the treatment of psychotic conditions. The dry latex is chewed by hunters and the soft gummy resin is commonly used in Northern Nigeria as a bird lime (Dalziel, 1937). The plant is popularly known as gamji among the Hausa tribes of Northern Nigeria where it has diverse utilisation. The cold water extract, decoction or powder of the root or bark is applied in various conditions such as sickle cell, insomnia, psychosis, depression and persons possessed by spirits (bori, ciwon inna or iska). The extract or decoctions are usually taken orally, while the powder is often mixed with food and eaten, or placed in burning charcoal and inhaled (Audu , 1989). The plant is also claimed to be useful as an analgesic and anti-psychotic (Muazzuam per. Communication).

To our knowledge, studies on the neuropharmacological properties of *Ficus platyphylla* have not been mentioned in any literature. The present study has therefore been designed, to evaluate the neuropharmacological effects of the methanol extract of *Ficus platyphylla* (F.P) stem bark so as to scientifically describe the potential values or otherwise of the extracts of the plant which is already in common use. Mainly, the behavioural effects of extract will be studied using locomotor activity, amphetamine induced hyperactivity, pentobarbitone induced sleep and haloperidol induced catalepsy.

CHAPTER TWO

CHAPTER TWO

2.0. MATERIALS AND METHODS

2.1. PLANT MATERIAL

The stem bark of *Ficus platyphylla* was collected from Kala,a in Hong Local Government of Adamawa state, Nigeria, in September 1997. The plant was identified and authenticated by Mr A. Ohaeri and Mallam I. Muazzam of the Department of Medicinal Plant Research and Traditional Medicine, NIPRD, Abuja. A voucher specimen (No 4035) was deposited at the NIPRD herbarium for future reference. The stem bark was cleaned and air dried for 7 days then milled into coarse powder. 80 g of the coarse powder was soxhlet extracted with 500 ml of methanol for 72h. The filtrate was freeze-dried and gave a yield of 8.2%w/w.

2.2. ANIMALS

Swiss albino mice (18-25 g) and adult Wistar rats (200-250 g) of either sex maintained at the Animal Facility Center of NIPRD, Abuja were used. Black ranger cockrels (obtained from Arewa Agricultural Enterprises Nig. Ltd. Zaria). The animals were housed in standard environmental condition of temperature, relative humidity and light. The animals were fed on standard diet (Pfizer feed, PLC Lagos) and water *ad libitum*.

All the records were transferred into a computer to facilitate analysis. Control and test experiments were performed in a quiet, temperature-controlled room (22 $\pm$ 1°C) and

between 8.30am to 4.00pm to avoid behavioural changes resulting from circadian rhythms.

2.3. CHEMICALS AND DRUGS

Methanol (Sigma, St Louis U.S.A) Sea salt (Sigma Chemical Co. U.K.),

Artemia salina Leach (brine shrimp eggs from Interpet Ltd., Dorking England), Sodium chloride (Fisher Scientific co. USA), Acetic acid (Hopkin and Williams England), Methylated spirit

Pentylenetetrazole(Sigma Chemical Co. U.S.A), Clonazepam (Sigma Chemical Co. U.S.A)

D-Amphetamine sulphate (Sigma Chemical Co. USA), Pentobarbitone sodium

Methanolic extracts of *Ficus platyphylla* stem bark.

Apomorphine Hydrochloride (Sigma Chemical Co. U.S.A)

Haloperidol (Sigma Chemical Co. U.S.A.)

Fresh egg albumin, Acetyl salicylic Acid

Emetine

2.4. EQUIPMENT

Small tank with perforated dividing dam to grow shrimp, cover and lamp(to attract shrimp) syringes (1ml, 5ml, 10ml) and needles, 96-well microplates (ICN flow U.K.), Micropipettes

LETICA Activity Cages (LE 886) and multicount (LE 3806, LETICA Spain), Am 1051 (Benwick electronics) Data loggers, Animal cages, Tally counters, Stop clock, Cotton wool, Tripple beam balance (Ohaus, New York, USA), Metler balance P165, Incubator,

Binocular microscope, 3cm and 9cm high blocks, Ugo Basile constant current electroshock machine (model 7800) with corneal electrodes, Claude Lyon voltage stabilizer, Plethysmometer (LETICA).

2.5. PHYTOCHEMICAL TESTS

Freshly prepared extract of the bark was chemically tested for the presence of alkaloids, glycosides, tannins, saponins, flavonoids, sterols etc using standard protocols (Trease and Evans, 1983).

2.6. TOXICOLOGICAL STUDIES

2.6.1. Brine Shrimp Lethality Bioassay (LC_{50})

The modified microwell cytotoxicity assay developed by Maclaughlin *et al.* (1988) was employed for this study. Brine shrimp *Artemia salina* lethality bioassay procedure was used to estimate cytotoxic effects and to facilitate the determination of biological activity of the preparation. Serial dilutions were made in the wells of 96-well microplates (ICN Flow, U.K.) in triplicate in 100 ul natural sea water obtained from the Atlantic ocean at Bar beach, Lagos. Control wells with sea water was included in each experiment. Three suitable dose levels ranging from 50-500 mg/ml of the extract were selected and tested in triplicate. Emetine, a cytotoxic alkaloid obtained from *Uragoga ipecacuanha* was employed as a reference drug in the study. A set of 3 experiments were performed in each case and the mean was determined. A suspension of brine shrimps containing 15 organisms in 100 ul was added to each well and the covered plate was incubated at room temperature (22-24°C) for 24 hours. The living shrimps usually display active mobility in the wells. Complete immobility was therefore regarded as death. The plates were examined under a binocular

microscope and the number of immobile shrimps in each well was counted against the total number in the well. LC_{50} values were then calculated.

2.6.2. Acute Toxicity Studies in Mice (LD_{50})

Toxicity studies were carried out in mice, in order to determine the mean lethal dose (LD_{50}) of the extract. The mice were starved of food but allowed free access to water for about 24h before being exposed to the extract. The extract was administered intraperitoneally and animals were observed for sign and symptoms of toxicity within 24hours. The determination of the LD_{50} was carried out using the method of Lorke (1983) in two stages. In stage one a preliminary estimate of the range of doses in which the LD_{50} could possibly fall was determined. In stage two further specific doses were administered to determine the actual LD_{50}. The final LD_{50} value is given by the square root of the product of the highest non-lethal dose and the lowest lethal dose ie the geometric mean of the doses for which 0/1 and 1/1 survival rates were found.

2.7. SPONTANEOUS MOTOR ACTIVITY TESTING

Spontaneous motor activities were recorded using both the LETICIA Activity Cage (LE 886) coupled to multicount (LE3806) and AM 1051 (Benwick electronics) Data logger. Adult mice of either sex were randomly divided into four groups of 6 mice per group. Three groups were given graded doses of the extract (25mg-100 mg/kg, i.p.). Animals in the remaining group received normal saline as control. Thirty minutes later, the animals were transferred individually to Letica Activity Cages (LE 886) connected to a Multicount (LE 3806) and after 1 min latency, activity counts were recorded for 6 minutes (Rakesh *et al.,* 1994; Wambebe *et al.,* 1997) at 30, 60,90 and 120 minutes. Similar studies were carried

out using the AM 1051 Data logger with two layers of infra-red sensors placed horizontally to monitor the mobile counts, static counts, rearing, counts, active time and mobile time. Activity records were taken for 6 minutes at 30, 60 and 90 minutes on the Data logger.

2.8. STUDIES ON AMPHETAMINE-INDUCED HYPERACTIVITY IN MICE

These tests were performed in adult mice of either sex weighing between 18 - 25g. They were randomly divided into three groups of 6 mice each. Two groups were pretreated with two doses of the extract (50 and 100mg/kg i.p respectively) while the other group received normal saline as control. Thirty minutes later, d-amphetamine (2mg/kg i.p) was administered to all the mice. The animals were transferred individually to LETICA Activity cages (LE 886) connected to a multicount (LE 3806) and after 1 min. latency, activity counts were recorded for 6 min. at 15, 30, 60, 90, and 120 minutes. The recorded data were transferred into a computer to facilitate analysis.

2.9. STUDIES ON AMPHETAMINE-INDUCED STEREOTYPE BEHAVIOUR IN MICE

Stereotyped behaviour is a perseverance, continuous, and apparently purpose-less activity during which there is absence of normal behaviour (Randrup and Munkvad, 1966a). Stereotyped behaviour can be induced in experimental animals using several drugs which include, amphetamine, apomorphine, ergometrine, piribedil etc and different species of animals may produce different stereotypies which may also vary among individuals of the same species (Amabeoku, 1989).

Adult mice of either sex weighing between 18 and 25g were used in this test. They were randomly divided into four groups of 6 mice each. Three groups were pretreated with graded doses of the extract (25 – 100 mg/kg i.p.), while the other group received normal saline as control. Thirty minutes later, d-amphetamine (2mg/kg i.p) was administered to all the mice. Signs of stereotypic behaviour that includes, sniffing, reciprocal forepaw treading/licking, jumping, cycling were observed and counted using hand tally counters for 2 hours (Randrup and Munkvad 1967; Nemeroff, 1980).

2.10. STUDIES ON APOMORPHINE INDUCED STEREOTYPE BEHAVIOUR IN MICE

Adult mice of either sex weighing between 18 and 25g were used. They were randomly divided into three groups of 6 mice each. Two groups were pretreated with two doses of the extract (25 and 50mg/kg i.p respectively), while the other group received normal saline as control. Thirty minutes later, apomorphine (2mg/kg i.p) was administered to the mice. Signs of stereotypic behaviour which include Sniffing, Jumping/Climbing, reciprocal paws treading/licking and cycling were observed and counted using hand tally counters for two hours (Randrup and Munkvad, 1967; Nemeroff, 1980).

2.11. STUDIES ON PENTOBARBITONE SLEEPING TIME IN RATS

The test was carried out in 3 groups of 5 rats each. Two groups received the two doses of the extract (50 and 100 mg/kg i.p respectively.), while the other group received normal saline as control. Thirty minutes later, pentobarbitone sodium (40mg/kg i.p.) was administered to each rat to induce sleep. Each rat was observed for the onset and

duration of sleep, with the criterion for sleep being loss of righting reflex (Miya *et al.*, 1973; Wambebe, 1985). The interval between loss and recovery from righting reflex was used as the index of hypnotic effect (Fujimori, 1965).

2.12. STUDIES ON HALOPERIDOL-INDUCED CATALEPSY IN RATS

Adult Wister rats of either sex weighing between 200 - 250g were used. The rats were handled for 3 - 5 days prior to behavioural testing. They were randomly divided into three groups of 6 rats each. Two groups were pretreated with two doses of the extract (25 and 50mg/kg i.p. respectively.), while the other group received normal saline as control. Haloperidol (2mg/kg i.p.) was administered to all the rats in each group thirty minutes after pretreatment with the extract and severity of catalepsy was measured every 30 minutes thereafter up to a total duration of 3 hours. Catalepsy of an individual rat was measured in a stepwise manner by a scoring method as described by (Khisti *et al.*, 1997). The method assessed the ability of an animal to respond to an externally imposed posture.

Step I: The rats were taken out of the home cage and placed on a table. They were pushed forward by a gentle touch on the back. If the rat failed to move when touched gently on the back or pushed, a score of 0.5 was assigned. Step II: The front paws of the rat were placed alternately on a 3-cm high block. If the rats failed to correct the posture within 15sec, a score of 0.5 for each paw was added to the score of the step I. Step III: The front paws of the rat were placed alternately on a 9cm high block. If the rat failed to correct the posture within 15 sec., a score of 1 for each paw was added to the scores of

step II and I. Thus, for an animal, the highest score was 3.5 (Cut-Off Score) and reflects total catalepsy.

2.13. SEIZURE STUDIES

2.13.1. Pentylenetetrazole - induced Convulsion (seizures) in Mice

Adult mice of either sex were randomly divided into four groups of 4 mice each. Two groups were given two doses of the extract (50 and 100mg/kg i.p. respectively), one group was given normal saline as control and the remaining one group received clonazepam (0.2mg/kg i.p.). Thirty minutes later, pentylenetetrazole (80mg/kg i.p.) was administered to all the mice. The onset and incidence of convulsion (seizure) were observed for 1 hour after administration of pentylenetetrazole, and death 24 hours after the experiment was also observed. Lack of tonic extension of the hindlimbs was regarded as no convulsion.

2.13.2. Electroshock induced Convulsion (seizures) in Chicks

Day-old black cockrels (35-45g) were randomly divided into three groups of 4 chicks per group. Two groups were given two doses of the extract (50 and 100mg/kg i.p respectively), while one group given normal saline served as control. Ugo Basile's electroconvulsive therapy (ECT) machine (model 7800) connected to Clande Lyons Voltage stabilizer with corneal electrodes was used to induce seizures in the chicks. The shock duration, frequency and pulse width were maintained at 0.8 second, 100 pulses per sencond and 0.4 ms respectively throughout the experiment. A current of about 48mA,

which produced tonic seizures in 70-90% of the control chicks, was used throughout the study to test the anticonvulsant property of the extract. Maximal electroschock was recorded when tonic extension of the limbs was produced.

2.14. STUDIES ON THE ANALGESIC EFFECT OF THE EXTRACT IN MICE

Adult mice of either sex weighing 18 - 25g were randomly divided into three groups of 6 mice each. Two of the groups were given two doses of the extract (25 and 50mg/kg i.p respectively), while the remaining group received normal saline as control. Acetic acid (300mg/kg i.p) was administered at 30 and 60 minutes after the administration of the extract. The number of writhings was recorded for a period of 5 minutes in each case.

2.15. STUDIES ON THE ANTI-INFLAMMATORY EFFECT OF THE EXTRACT IN RATS

The method of Winter *et al.,* (1962) was used. Rats of either sex were fasted for 12 hours and deprived of water only during the experiment. Deprivation of water was to ensure uniform hydration and to minimize variability in oedematous response (Winter *et al.,* 1963). Inflammation of the hind paw was induced by injecting 0.1 ml fresh egg albumin (phlogistic agent) into the subplantar surface of the right hind paw. The control group was given normal saline, the second group received acetyl salicylic acid (150 mg/kg) while the remaining three groups received extract at doses of 25,50 and 100mg/kg i.p respectively. The measurement of foot volume was done by a displacement technique using the Plethysmometer (LETICA), immediately before and every 20 min after the injection of egg albumin for 2 hours. The inhibitory activity was measured by subtracting the mean paw

volume of the treated rats before the injection from the mean paw volume after the egg albumin injection at each time interval and comparing the results with the control.

2.16. STATISTICAL ANALYSIS

Results were expressed as mean $\pm$ SEM. The significance of difference between means was tested by the Students *t*-test and results were regarded as significant when $P<0.05$.

CHAPTER THREE

CHAPTER THREE

3.0. RESULTS

The phytochemical screening revealed the presence of flavonoids, condensed tannins and saponins.

3.1. Brine Shrimp Lethality Bioassay (LC_{50})

The LC_{50} of 113.7(g/ml was estimated. Most biologically active compounds have LC_{50} less than 1000ug/ml in this model (Maclaughlin *et al.*, 1988).

3. 2. Acute Toxicity Studies in Mice (LD_{50})

The result of LD_{50} of the extract is shown on Table 1. In stage one of the study the mice showed a 100% survival rate for the three selected doses of the extract. In the second stage of the study, the mice also showed 100% survival rate in all the selected doses. The LD_{50} of the extract was therefore estimated to be greater than 2000mg/kg, i.p. However, general depression and dyspnoea were observed, which appeared to be dose-dependent. All the mice recovered from the effects of the extract within 48 hours and remained normal throughout the 14 days observation period.

3.3. Effects of the Extract on Spontaneous Motor Activity in Mice

The extract (25-100mg/kg, i.p) caused a significant dose and time dependent decrease in spontaneous motor activity in mice. (Table.2, Fig.1.). It significantly attenuated the total

mobile, static and rearing activities as well as active and mobile times in mice (Table 3). The effects were dose and time dependent.

3.4. Effects of the Extract on Amphetamine-Induced Hyperactivity in Mice

The extracts (50-100mg/kg, i.p.) significantly ($P<0.001$) attenuated amphetamine induced hyperactivity in mice. The decrease in activity is dose and time dependent. (Table 4, Fig.2.)

3.5. Effects of the Extract on Amphetamine-Induced Stereotype Behaviour in Mice

The extract (25-100 mg/kg i.p.) significantly ($P<0.05$, $P<0.001$) attenuated amphetamine-induced stereotyped (Sniffing, Jumping/Climbing, Forelimb/Hindlimb licking, and cycling) behaviour in mice. The decrease in all the stereotyped behaviour are dose and time dependent (Table 5, Fig. 3.)

3.6. Effects of the Extract on Apomorphine-Induced Stereotype Behaviour in Mice

The extract (25-50mg/kg,) significantly ($P<0.001$) attenuated apomorphine (2mg/kg, i.p) induced stereotyped behaviour (Sniffing, Jumping/Climbing, forelimb/Hindlimb licking, and Cycling) in mince, the effects were dose dependent (Table 6 Fig.4.)

3.7. Effects of the Extract on Pentobarbitone-Induced Sleep in Rats

The extract (50-100mg/kg i.p) significantly ($P<0.001$) prolonged the duration of pentobarbitone induced sleep in rats dose dependently, but did not influence the onset of sleep at the doses tested. (Table 7, Fig. 5).

3.8. Effects of the Extract on Haloperidol-Induced Catalepsy in Rats

The extract (25-50mg) induced catalepsy and significantly ($p<0.05$) exacerbated haloperidol (2mg/kg i.p)-induced catalepsy (Table 8, Fig.6.,7.). The effects of the extract on haloperidol-induced catalepsy was dose and time dependent. The optimum cataleptic response was evident at 30 minutes of haloperidol (2mg/kg,i.p) administration and reached to a peak at 150 minutes. Both doses of the extract reached peak effect at 120 minutes.

3.9. Effects of the Extract on Pentylenetetrazole-Induced Seizures in Mice

The extract reduced the incidence of pentylenetetrazole (80mg/kg i.p) induced seizures and abolished convulsion with tonic hindlimb extension but did not have effect on the on set of clonic jerks. The mortality was abolished and there was 100% protection. Clonazepam (0.0002mg/kg i.p) on the other hand, protected the mice against all the episodes of convulsion . (Table 9)

3.10. Effects of the Extract on Electroshock-Induced Seizures in Chicks

The extract(50-100mg/kg i.p) did not protect the chicks against electroshock seizures (Table 10). The seizure episodes and mortality were not affected by the extract.

3.11. Analgesic Effect of the Extract on Acetic Acid-Induced Pain in Mice

The extract (25-50mg/kg i.p) significantly ($P<0.05$) attenuated acetic acid (300mg/kg i.p) induced pain in mice. The analgesic effect of the extract was dose and time dependent (Table 11, Fig.8.)

3.12. Anti-inflammatory Effect of the Extract in Rats

The result shows that the i.p administration of the extract attenuated the inflammation (edema) of the hind paw induced by the fresh egg albumin, especially at the doses of 50 and 100mg/kg. There was no significant difference between the effects at the tested doses (25,50 and 100mg/kg i.p) and acetylsalicylic acid (150mg/kg i.p). (Table 12, Fig.9)

TABLE 1 : Lethal Dose (LD_{50}) of the Extract in Mice

Extract	Stage 1		Stage 2	
	Dose(mg/kg)	% Survival	Dose (mg/kg)	% Survival
F.P.	10	100	1200	100
	100	100	1500	100
			1800	100
	1000	100	2000	100

LD_{50}>2000mg/kg

TABLE:2 **Effects of the Extract on the Spontaneous Motor Activity in Mice. Gross Activity Recording from LETICA Activity Cage (LE886)**

Drug/Dose (mg/kg)	Mean activity Counts				
	0	30min.	60min.	90min.	120min.
Normal Saline	366.5±17.7	309±15.5	239.5±8.8	242.5±7.4	328±17.0
F.P (25)	366.5±17.7	268±14.0	168±7.1*	115±6.4*	140.5±3.1*
F.P (50)	366.5±17.7	248±13.5	159±6.9*	88.5±2.2*	77±3.1*
F.P (100)	366.5±17.7	128.5±5.7*	9.9.5±4.3*	86.5±3.5*	73.5±2.1*

Data Presented as Mean ± SEM
*Are significantly different from control at $P< 0.05$ Student's t-test.
n= 6.

Fig. 1 Effects of the extract on the spontaneous motor activity in mice.

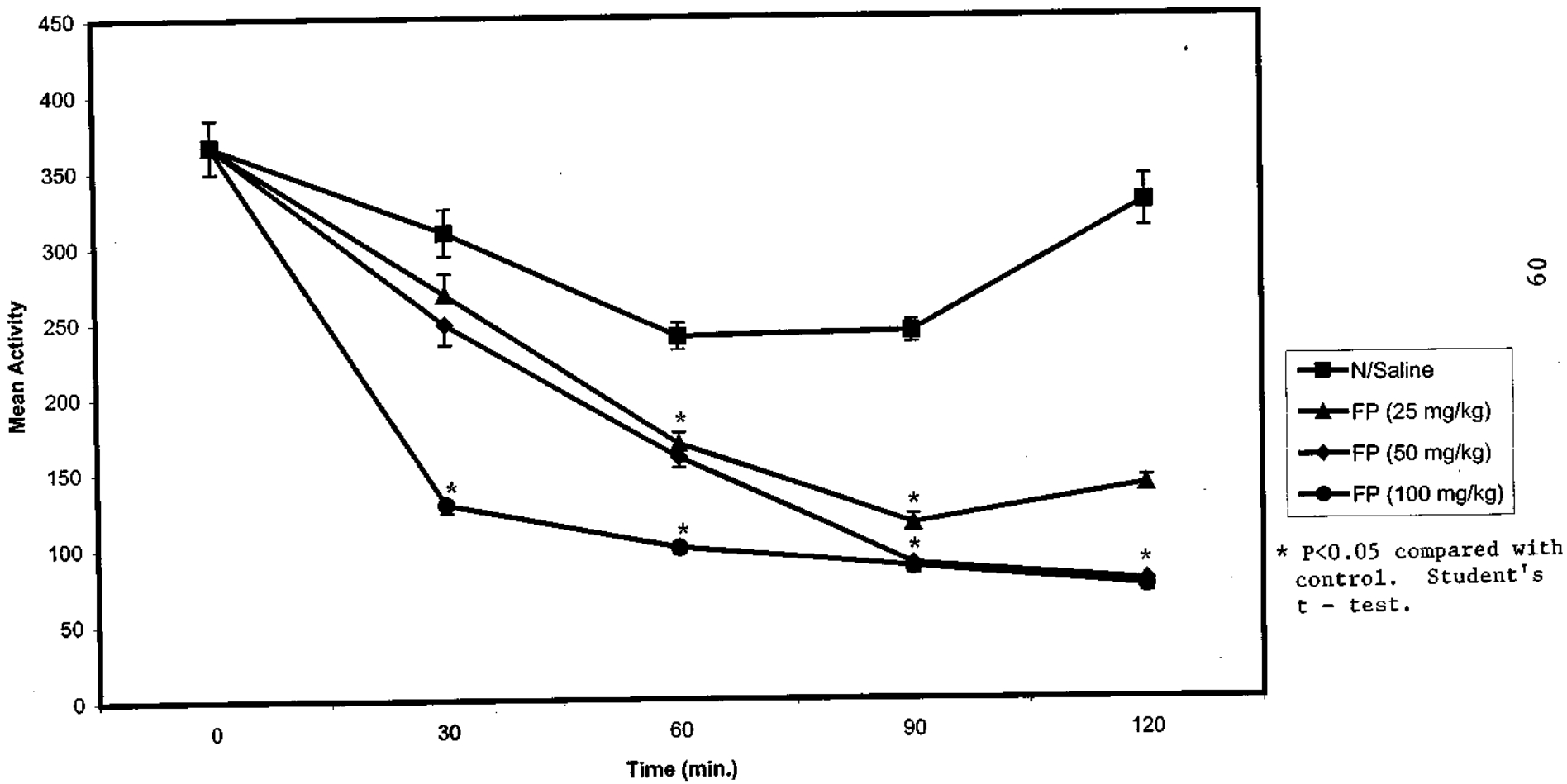


Table 3: Effects of the extract on locomotor activity in mice.
Reading from AM1051 Data Logger.

		Mobile Counts		Static Counts		Rearing Counts		Active Time		Mobile Time	
Drug/Dose (mg/kg)	Time (mins)	Slow	Fast	Slow	Fast	Slow	Fast	Time(sees)	%	Time(sees)	%
N/Saline	0	174±9.5	342.5±40	201±14.9	189±30.4	179.5±5	162±44	259.0±25.5	86±4.5	106±10.5	35±4.0
	30	238±6.3	542±9.6	150.5±6.9	136±8.7	214±10.0	167±8.1	261.5±16.8	87.0±5.6	149.0±10.8	49.5±7.9
	60	136±2.8	256±4.8	149±8.7	133±7.8	173.5±8.7	111.0±9.9	213.6±15.3	70.5±1.2	93.5±3.2	31.0±1.1
	90	151±5.6	274±8.6	145±4.3	112±10.0	210.5±9.6	169.0±10.6	226.5±13.7	75.5±7.9	89.5±5.1	29.5±1.8
F.P(50)	0	174±9.5	342.5±40	201±14.9	189±30.4	179.5±5.0	162±44	259.0±25.5	86±4.5	106±10.5	35±4.0
	30	131±2.9	252±6.6**	114±10.6	120.43	126.5±9.8*	99.5±9.0*	166.0±16.0*	55.5±5.7*	73.5±8.9*	24.5±3.0
	60	77±3.9*	115±5.2**	103±6.9*	104±5.6*	72.0±7.0*	85.5±7.7	135.0±12.5*	43.5±2.7*	48.0±9.5*	16.0±3.2
	90	44±4.9*	97±10.0	121±8.9	47±6.7*	55.0±2.2*	48.5±5.1*	126.5±12.4*	42.0±7.5*	36.0±4.6*	11.5±1.5
F.P(100)	0	174±9.5	342.5±40	201±14.9	189±30.4	179.5±5.0	162±44	259±25.5	86±4.5	106±10.5	35±4.0
	30	112±5.1*	218.5±8**	94.5±14*	114±2.9	82.5±10**	93.0±9.3*	142±10.2*	47.0±3.4*	70.0±0.72*	23.5±0.24
	60	56±8.1*	88±6.4**	85±2.5*	49.5±7.5*	59±8.6	51.0±7.1*	115.0±18.9*	38.0±6.3*	47.0±10.4*	15.5±3.5
	90	38±4.7*	63±5.8**	70±6.5	33±7.9*	25.5±9.3**	12.0±5.5**	84±13.8**	27.0±4.0*	24.0±10.4**	8±2.8

Data Presented as Mean ± SEM

***,** Are Significantly different from control at P< 0.05 and P< 0.001 respectively, Student's t-test**

n = 6.

TABLE:4 **Effects of the Extract on Amphetamine-induced Hyperactivity in Mice. Gross Activity Recordings from LETICA (LE 886)**

	Mean activity (counts)					
Drug/dose (mg/kg)	0	15 min	30 min	60 min	90 min	120 min
N/Saline	381.0 ± 12.2	494.5 ± 15.3	535.5 ± 13.5	490.5 ± 19.2	482.0 ± 12.7	489.0 ± 11.4
F.P(50)	381.0 ± 12.2	90.5 ± 2.6*	71.5 ± 3.1*	50.0 ± 1.8*	46.5 ± 2.2*	48.5 ± 2.0*
F.P (100)	381.0 ± 12.2	67.0 ± 3.1*	56.5 ± 1.3*	32.0 ± 1.0*	40.5 ± 1.2*	31.5 ± 1.0*

All the groups received Amphetamine 2 mg/kg i.p.
Data presented as Mean± SEM
*Are significantly different from control at $P < 0.001$ **Student's t-test.**
n = 6.

Fig. 2: Effects of the extract on amphetamine induced hyperactivity in mice.

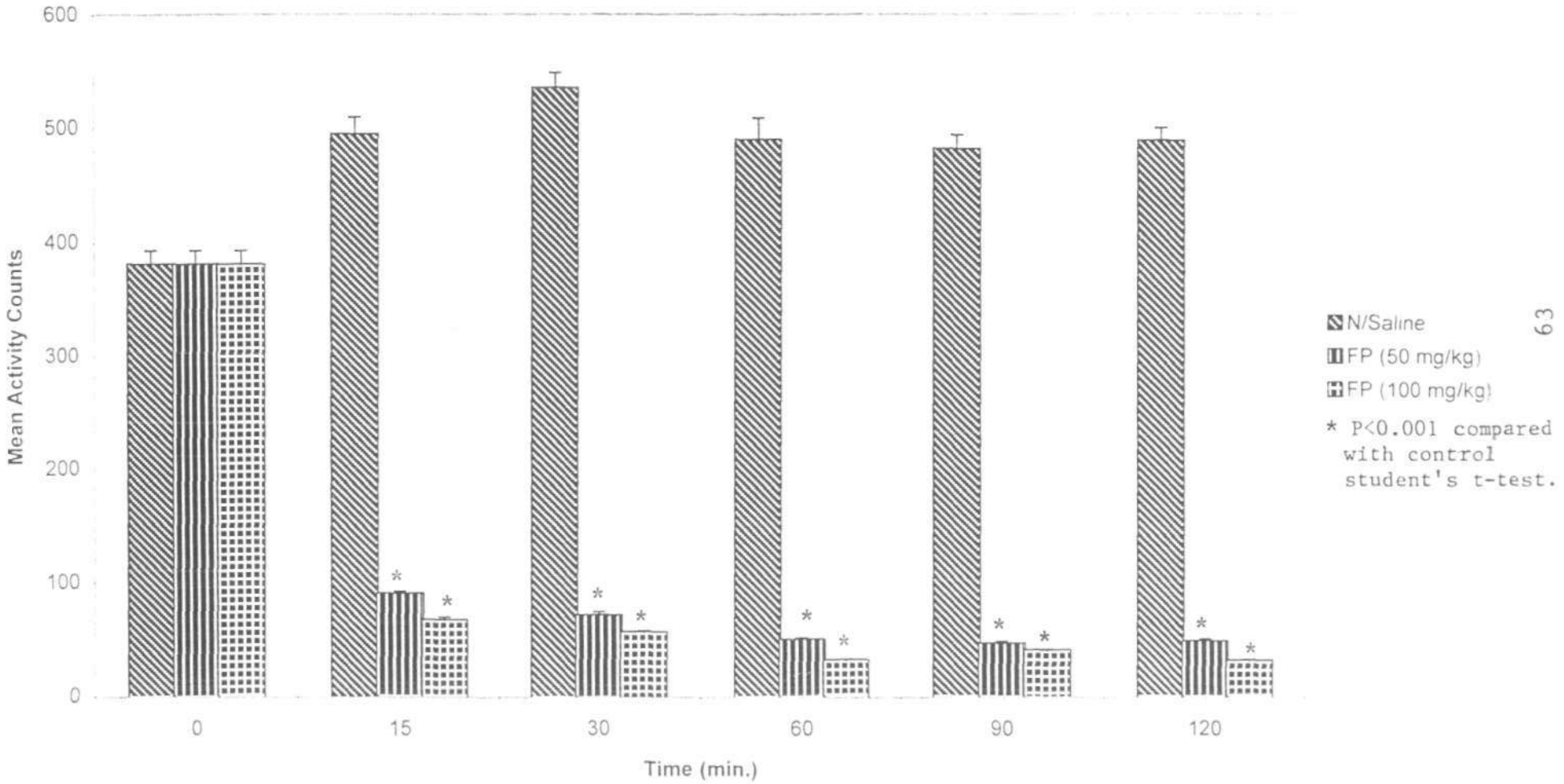


TABLE: 5 **Effects of the Extract on Amphetamine - induced Stereotype Behaviour in Mice.**

	Episodes			
Drug/Dose(mg/kg)	Sniffing	Jumping/Climbing	Forelimb/Hindlimb licking	Cycling
N/Saline	603.5 ± 8.9	494.0 ± 11.2	1481 ± 30.7	348.5 ± 3.7
F.P(25)	342.5 ± 2.6*	279.0 ± 2.0*	564.0 ± 4.6*	53 ± 1.4**
F.P (50)	178.5 ± 2.1**	183.0 ± 0.9*	344.5 ± 6.6*	47.5 ± 0.9**
F.P (100)	69.0 ± 1.0**	80.5 ± 1.6**	251.5 ± 8.0**	46.0 ± 1.7**

All the groups received amphetamine 2mg/kg i.p
Data presented as Mean ± SEM
* P<0.05; ** P<0.001 when compared with respective controls
n = 6 for all groups

Fig. 3: Effects of the extract on amphetamine stereotype behaviour in mice.

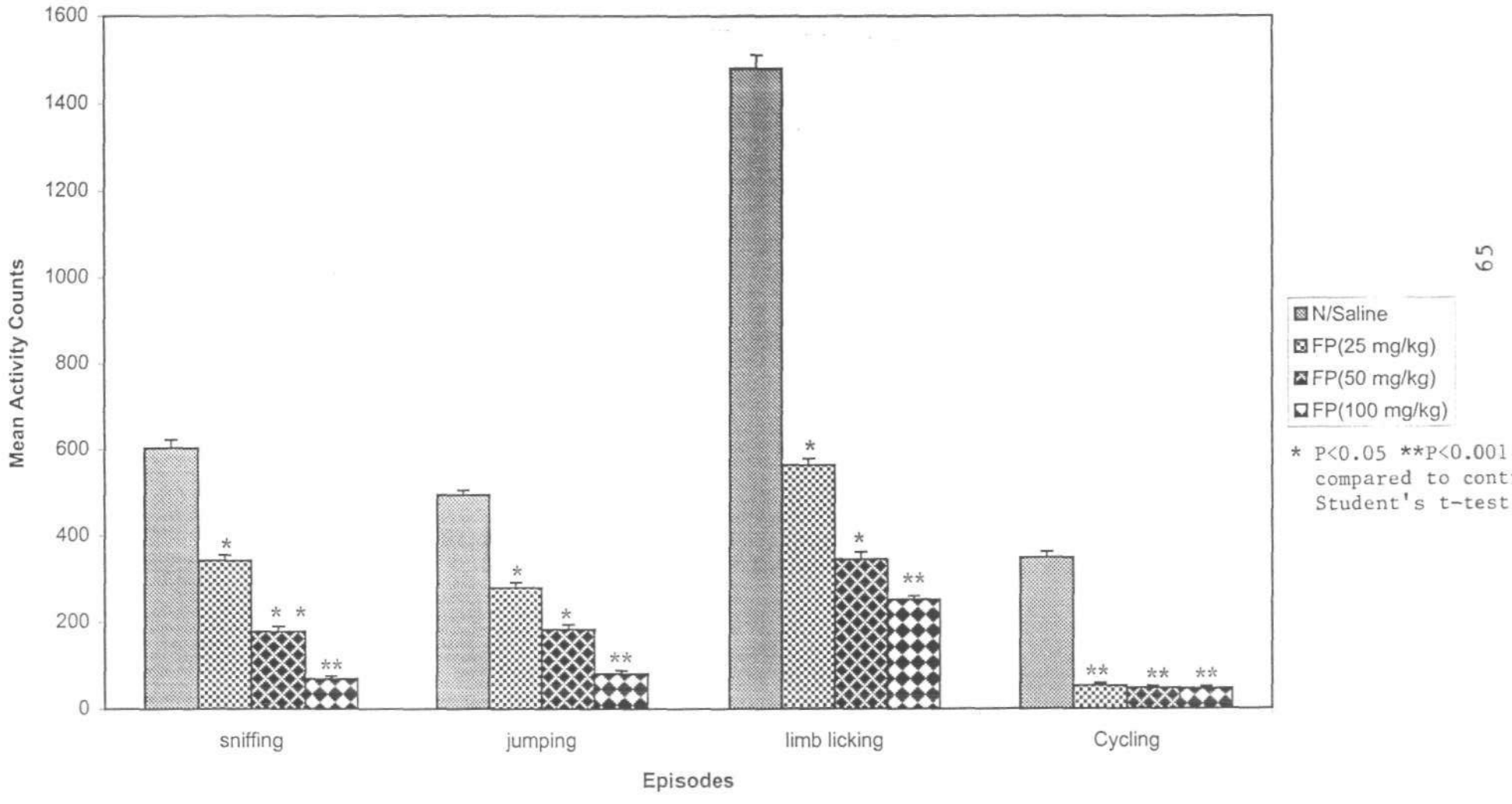


TABLE: 6 **Effects of the Extract on Apomorphine - induced Stereotype Behaviour in Mice**

Drug/dose (mg/kg)	Sniffing	Jumping/Climbing	Forelimb/Hindlimb licking	Cycling
N/Saline	1010.33 ± 25.6	480.0 ± 10.2	408 ± 8.6	16.0 ± 0.9
F.P. (25)	990.0 ± 21.3	252.0 ± 5.0*	224.0 ± 3.5*	5.3 ± 0.4*
F.P (50)	667.7 ± 9.7*	122.3 ± 2.1*	34.3 ± 0.8*	0

All the groups received apomorphine 2mg/kg i.p
Data presented as Mean ± SEM
*Are significantly different from control at P< 0.001 Student's t-test.
n = 6

Fig. 4: Effects of extract on apomorphine induced stereotype behaviour in mice

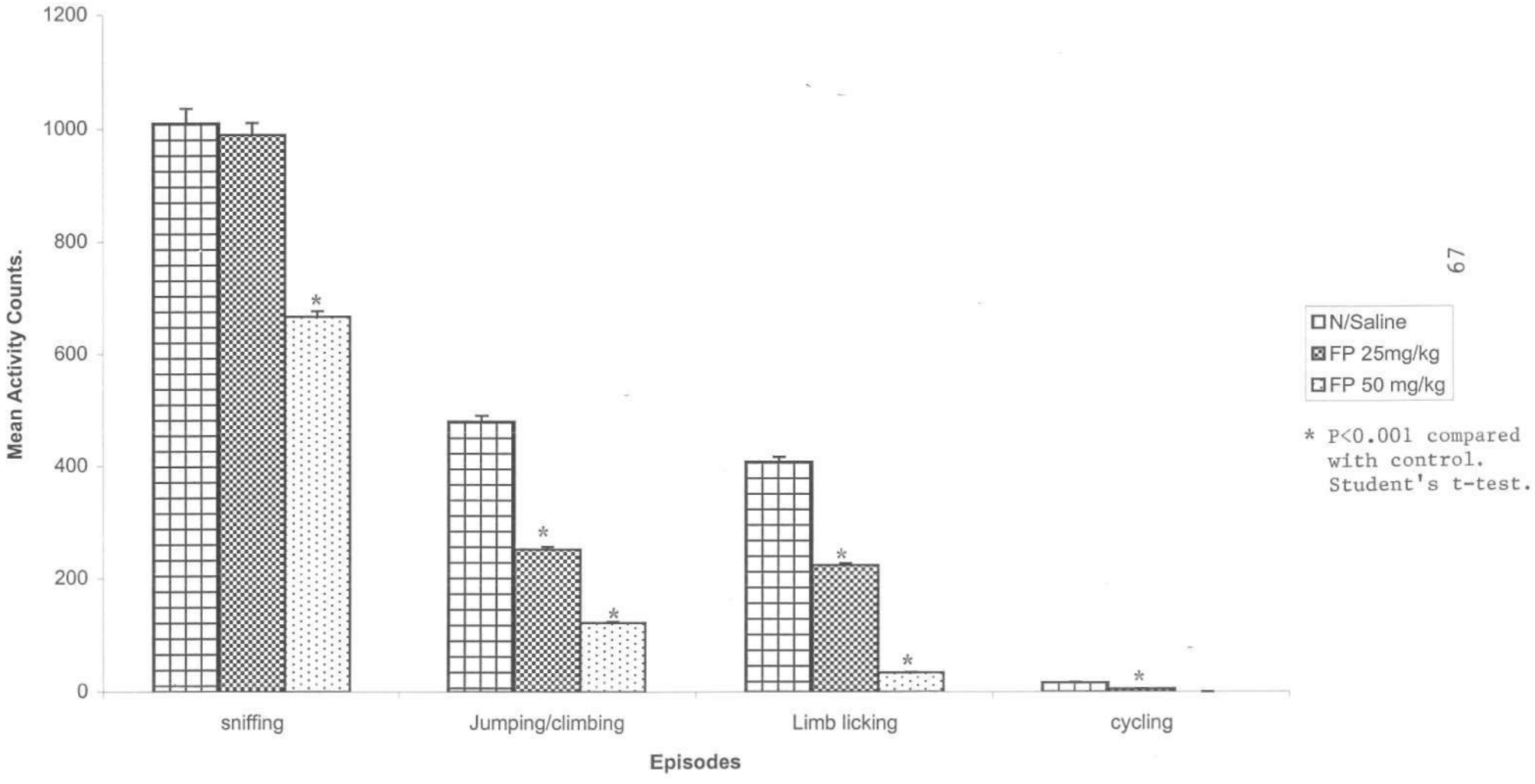


TABLE:7 **Effects of the Extract on Pentobarbitone Sleeping Time in Rats**

Drug/Dose (mg/kg)	Onset of sleep (min.)	Duration of sleep (min.)
N/ Satine	4.0 ± 0.2	70.5 ± 1.0
F.P(50)	4.0 ± 0.3	94.0 ± 1.7*
F.P (100)	4.0 ± 0.2	125.0 ±2.4*

All the groups received pentobarbitone sodium 35mg/kg i.p
Data presented as Mean ± SEM
*Are significantly different from control at $P< 0.001$ Student's t-test.
n = 5

Fig. 5 Effects of the extract on pentobarbitone sleeping time in rats.

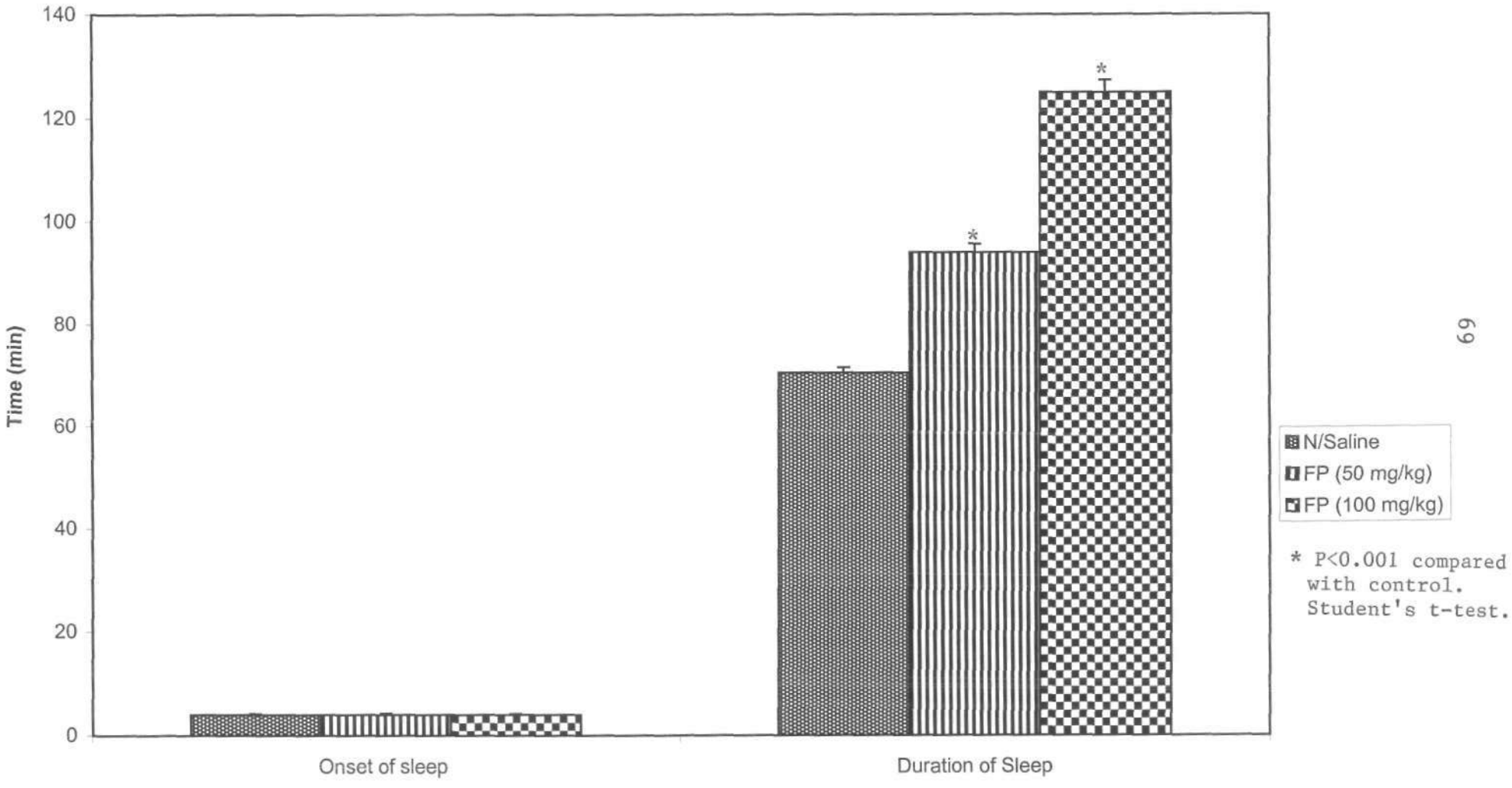


TABLE:8 **Effects of the Extract on Haloperidol - induced Catalepsy in Rats**

	Mean Cataleptic Score					
Drug/dose (mg/kg)	30 minutes	60 minutes	90 minutes	120 minutes	150 minutes	180 minutes
N/ Saline + Haloperidal (2)	0.3 ± 0.1	0.5 ± 0.10	1.16 ± 0.3	2.5 ± 0.2	2.83 ± 0.5	2.83 ± 0.5
F.P (25)	0.3 ± 0.12	1.33 ± 0.15	1.50 ± 0.3	2.16 ± 0.5	2.50 ± 0.4	2.50 ± 0.4
F.P (50)	1.2 ± 0.2	1.50 ± 0.25	1.83 ± 0.35	2.67 ± 0.3	2.83 ± 0.5	2.83 ± 0.5
F.P (25) + Haloperidal 2	1.66 ± 0.8	1.83 ± 0.5*	2.67 ± 0.5*	3.0 ± 0.4	3.17 ± 0.3	3.33 ± 0.5
F.P (50) + Haloperidal (2)	1.83 ± 0.5*	2.0 ± 0.4*	3.17 ± 0.1*	3.5 ± 0.0*	3.5 ± 0.0	3.5 ± 0.0

Data presented as Mean ± SEM
*Are significantly different from control at P< 0.05 Student's t-test.
n = 6.

Fig. 6: Effects of the extract on haloperidol induced catalepsy in rats.

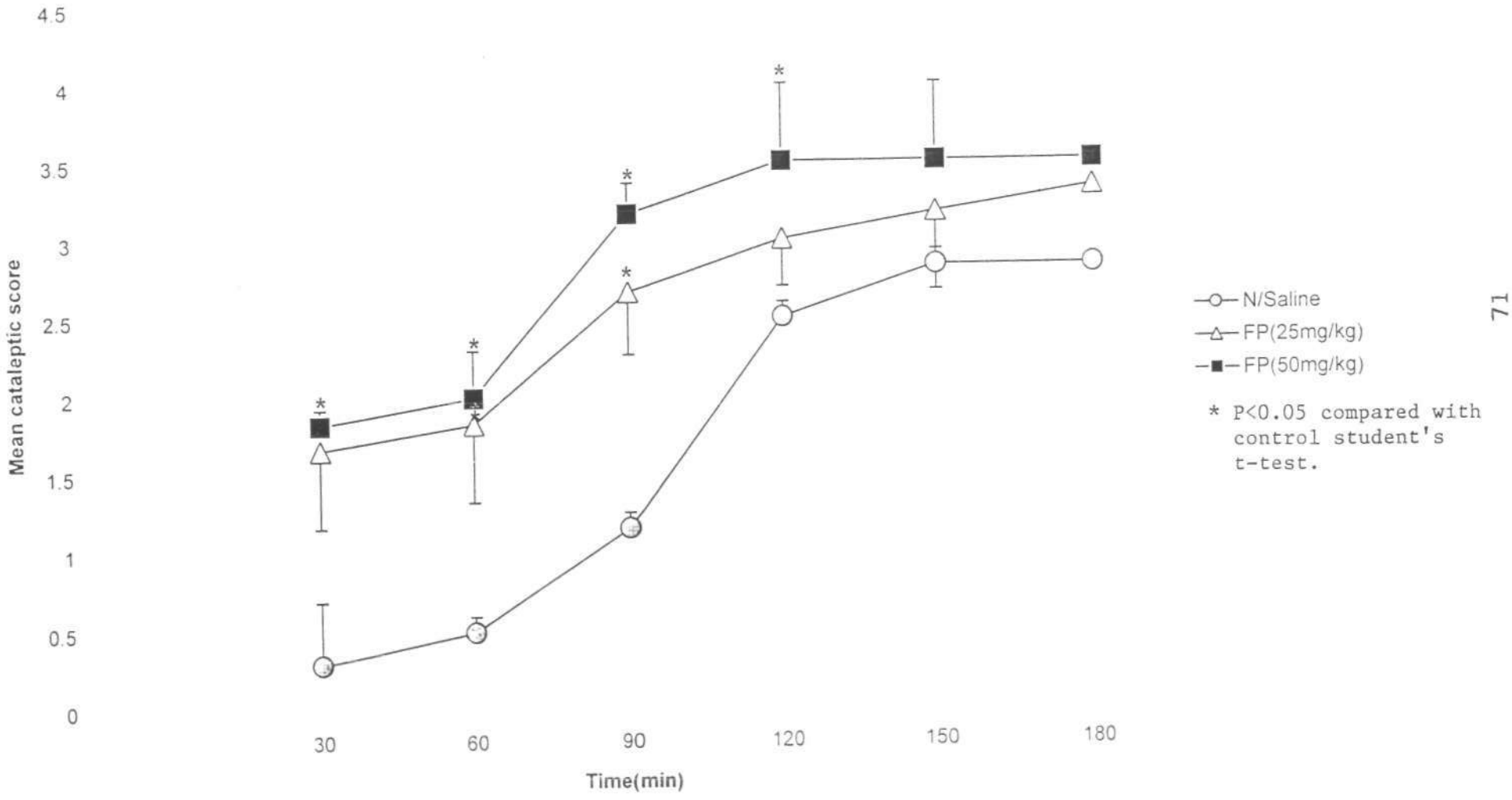


Fig. 7 Cataleptic effect of the extract in rats

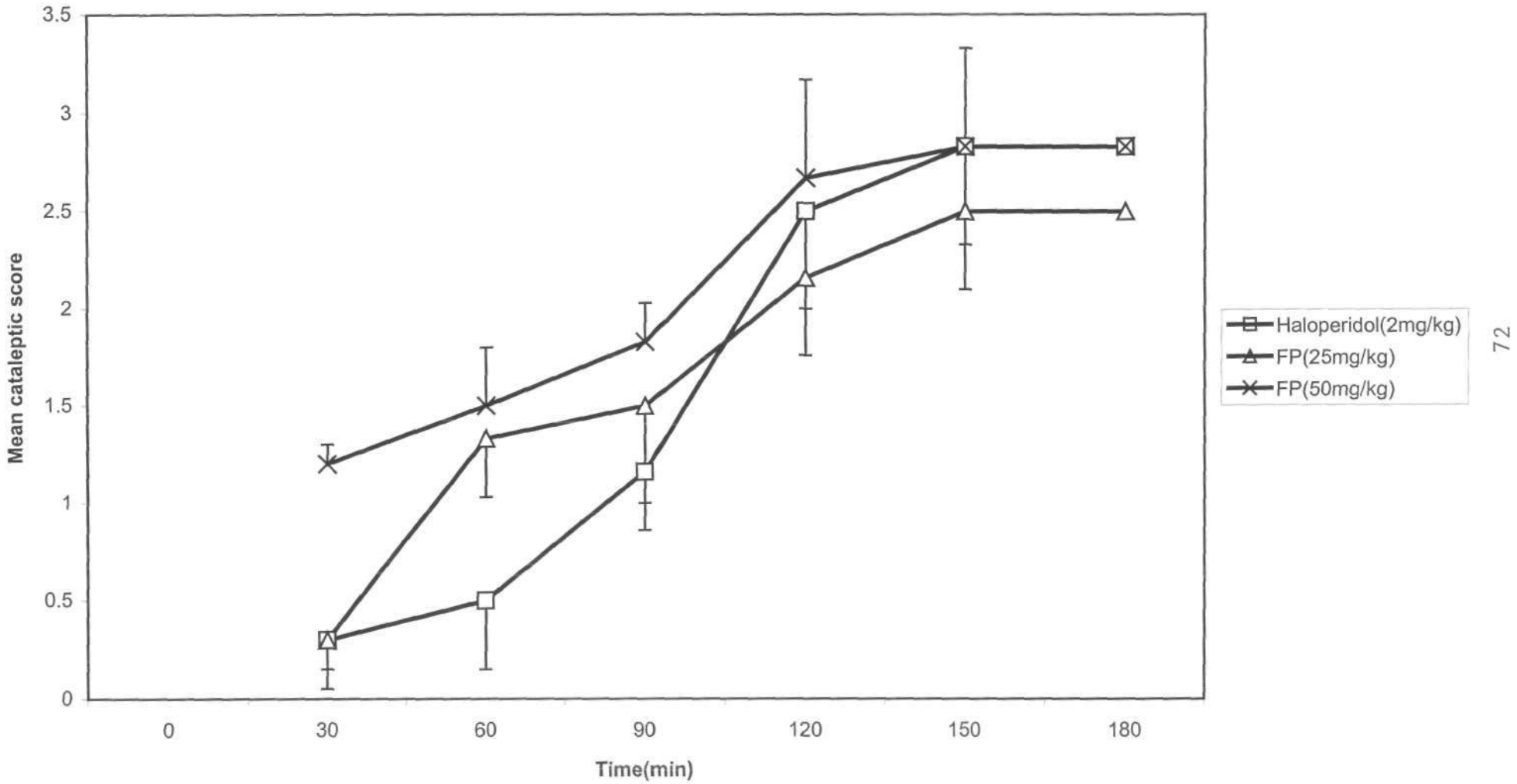


TABLE 9 **Effects of the Extract on Pentylenetetrazole-induced Seizures in Mice**

Drug (doses mg/kg)	Mean Onset of Seizures (min) Clonic jerks (Myoclonus)	Tonic hind limb extension	% Protection	Mortality
Normal Saline	1.3±0.10	3.75±0.85	0	4
Clonazepam (0.0002)	0	0	100	0
F.P (50)	1.2±0.9	0	100	0
F.P(100)	1.3±0.25	0	100	0

All the groups received pentylenetetrazole (80 mg/kg i.p)

Data presented as Mean ± SEM
n = 4.

TABLE 10 **Effects of the Extract on Electroshock Convulsion in Chicks**

Drug/Dose (mg/kg)	No.convulsed / No.used	% Tonic seizures	% Mortality	P value
Normal Saline	3 /4	75	0	
FP (50)	3 / 4	75	0	NS
FP (100)	4 / 4	100	0	Ns

NS= Not significantly different from control (chi squared test).
n=4

TABLE:11 Analgesic Effect of the Extract in Mice

Drug/dose (mg/kg)	Pretreatment time (min)	Writhing counts (mean ± s.e.m)
Normal Saline	0	21.0 ± 0.76*
F.P (25)	30	4.0 ± 0.85*
	60	3.5 ± 0.62*
F.P (50)	30	2.5 ± 0.85*
	60	2.0 ± 0.71*

All the groups received Acetic acid 300 mg/kg i.p.
*Are significantly different from control at $P < 0.05$ Student's t-test.
n = 6.

Fig. 8: Analgesic effect of the extract in mice.

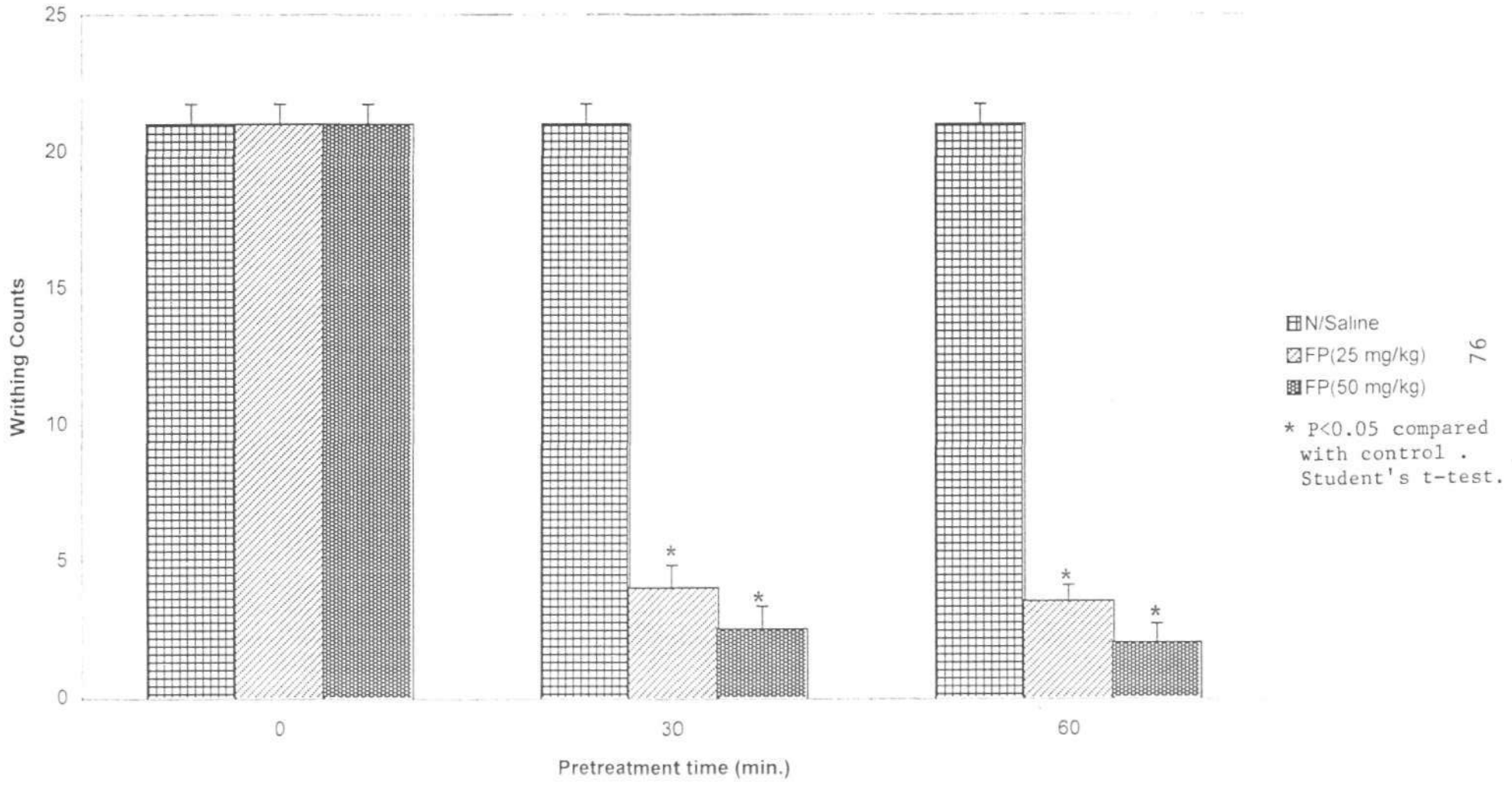


TABLE: 12 Anti-inflammatory Effect of the Extract in Rats

Drug/Dose (mg/kg)	Volume of Oedema					
	20min	40min	60min	80min	100min	120min
Normal/Saline	0.46±0.01	0.53±0.02	0.61± 0.02	0.60± 0.03	0.58±0.09	0.62±0.07
Acetyl Salicylic acid (150)	0.29±0.01	0.39±0.04	0.46±0.03	0.45±0.05	0.48±0.03	0.45±0.03
F.P(25)	0.42±0.05	0.64±0.06	0.58±0.02	0.61±0.06	0.51±0.03	0.51±0.04
F.P(50)	0.31±0.04	0.57±0.04	0.51±0.03	0.45±0.03	0.47±0.03	0.42±0.01
F.P(100)	0.02±0.03	0.52±0.02	0.47±0.01	0.41±0.04	0.45±0.04	0.41±0.03

Data Presented as Mean ± SEM
n=4

CHAPTER FOUR

CHAPTER FOUR

4.0. DISCUSSION

Generally the data presented here suggest that the crude methanolic extract of *Ficus Platyphylla* stem bark may contain psychoactive substances which are sedative in nature. The substances have potential values in the management of psychotic and convulsive disorders. The extract significantly reduced spontaneous motor activity (SMA) in mice. This model has been used in laboratory animals to evaluate the gross behavioural effects of drugs (Hsieh *et al.,* 1991; Carpenedo *et al.,* 1994; File and Fermandes 1994). The total mobile, static, and rearing counts as well as the active and mobile times were reduced profoundly. Many groups of psychotropic compounds, can cause reduction in SMA in laboratory animals. For instance, nearly all the neuroleptic agents used in psychiatry diminish SMA in all species of animals including man (Baldessarini,1990). Similarly, Lowe *et al.* (1978) reported that the tricyclic antidepressants (TCA's) decrease the SMA, and impair both acquisition and performance of conditioned responses. The extract significantly attenuated amphetamine-induced hyperactivity and stereotype behaviour in mice. Amphetamine hyperactivity and stereotyped behaviour have been used as behavioural model in screening drugs for anti-psychotic and antiparkinsonian properties (Janssen, 1970; Costall *et al.,* 1974). These workers demonstrated that a strong correlation exists between the anti-amphetamine activity of neuroleptics and their clinical efficacy in the treatment of psychoses. Amphetamine produces its effects by directly and indirectly stimulating postynaptic dopamine receptors (Stolk and Rech, 1970). These

effects are thought to be produced via dopaminergic mechanisms, particularly at the striatal pathways (VanRossum, 1970; Scheel-Kruger, 1971; Creese and Iverson, 1974). These behavioural effects of amphetamine are antagonised by neuroleptics, which are widely believed to be dopamine (D2) receptor antagonists (Amabeoku, 1989). Thus the results of this study suggest that the extract produce similar effects to neuroleptics, thereby supporting its use in traditional medicine for this purpose. Similarly, the extract significantly attenuated apomorphine-induced stereotyped behaviour in mice dose dependently. According to Stolk and Rech (1970), apomorphine acts directly on the postsynaptic dopamine receptors to induce hyperactivity and stereotyped behaviour. These behavioural effects of apomorphine could also be masked by neuroleptics. The effects of the extract against amphetamine and apomorphine suggest that the extract may interfere with dopaminergic neurotransmission in a manner that may be beneficial in psychotherapy (Nemeroff, 1980). The finding also correlate with the use of this extract in traditional medicine to calm hysteric patients (*bori*). This property may be useful in aggressive and over reactive psychotic patients.

The extract significantly prolonged the duration of pentobarbitone induced sleep in rats dose-dependently. This finding further demonstrates the sedative nature of the extract and its usefulness in calming excited individuals. Endogenous neurotransmitters in the brain particularly dopamine, have been suggested to play an important role in sleep mechanisms. Osuide and Wambebe (1980) reported that increased central dopamine receptor activity might be involved in both behavioural alertness and the waking process from pentobarbitone sleep in chicks. It is probable that the extract prolongs the duration

of pentobarbitone induced sleep in the rats via dopaminergic pathways or some other mechanisms that may be related to sleep.

The extract induced catalepsy and significantly exacerbated haloperidol induced catalepsy in rats in a dose-related manner. Catalepsy is a trance-like state of self-hypnotic sleep during which there is long-term maintenance of an animal in an abnormal posture. The ability of an agent to induce catalepsy is widely used as an experimental indicator of neuroleptic or anti-psychotic potency (Janssen, 1970). The significant cataleptic effects of the extract in this study therefore strengthens the speculation that it might possess a potent antipsychotic activity.

Although, neuroleptic-induced catalepsy is primarily due to the blockade of dopaminergic neurotransmission (Janssen *et al.,* 1965; Snyder *et al.,* 1974; Baldessarini, 1990), a number of other neurotransmitter systems indirectly influence this response. Facilitation of noradrenergic neurotransmission for instance attenuates, while that of serotonergic neurotransmission exacerbates neuroleptic induced catalepsy (Khisti *et al.,* 1997). Potentiation of haloperidol-induced catalepsy by the extract in this experiment may well be a simple synergistic effect of the extract and haloperidol.

The extract markly attenuated acetic acid induced pain in mice dose dependently. The involvement of dopamine receptors in the modulation of pain perception has been reported (Akil and Liebeskind, 1975; Bensreti *et al.,* 1983). Bensreti *et al.* (1983) reported that stimulation of D2 receptors facilitates analgesia while D1 receptor

stimulation evokes hyperalgesia responses. However, Gonzalez *et al.* (1985) observed that although, stimulation of D2-receptors evokes antinociception and D1-hyperalgesic responses, in the presence of D2 antagonist, stimulation of D1 receptor produces antinociception and not hyperalgesia. This is consistent with the work reported by Rubinstein *et al.* (1988), that there is interdependence between the two dopamine system. Opioid receptors have been linked to dopamine receptors in the striatum (Headley and Oshaughnessy, 1985) and it has been reported that central dopamine function may modulate the analgesic activity of morphine (Bensreti and Sewel, 1983). These workers observed that apomorphine, a directly acting dopamine agonist, significantly attenuated morphine antinociception and haloperidol, a potent dopamine receptor antagonist, markedly augmented the activity of morphine. Flower *et al.* (1985) on the other hand, reported that, prostaglandins are associated particularly with the development of pain that accompanies injury or inflammation and induction of hyperalgesia (with normally painless mechanical or chemical stimulation) seems to be a typical response to low concentrations of prostaglandins. According to Perl (1976), prostaglandin-induced hyperalgesia results from lowering of the threshold of the polynodal nociceptors of C-fibres. The non narcotic agents do not affect the hyperalgesia or pain caused by direct action of prostaglandins, which is consistent with the notion that it is their synthesis that is inhibited to produce antinociception (Flower *et al.,* 1985). From the forgoing it may be concluded that the dose dependent attenuation of acetic acid induced nociception by the extract may be via central mechanisms involving dopaminergic systems or may possibly act peripherally by the inhibition of prostaglandins synthesis.

The results of the anti-inflammatory studies suggest that the extract possesses an anti-inflammatory principle of high potency. There are several mechanisms involved in the anti-inflammatory activity of drugs. They include the endogenous release of glucocorticoids, interaction with prostaglandin biosynthesis, interaction with tachykinin or other inflammatory mediators etc (Barnes *et al.,* 1990). Furthermore, there are reports concerning the anti-inflammatory effects of flavonoids and steroids (Panthong *et al.,* 1989; Recio *et al.,* 1995). It is difficult to ascertain from this data, the exact mechanism by which the extract achieved the anti-inflammatory activity. It is possible that the flavonoids present in the extract might contribute to the anti nociceptive and anti-inflammatory effects of *Ficus Platyphylla*.

The extract reduced the incidence of pentylenetetrazole induced seizure. It protected the mice against tonic hindlimb extension. This finding suggests that the extract is active against chemically induced seizures and may be useful in the management of convulsive disorder. The results also butress the hypothesis that there is a sedative principle in the extract which is responsible for some of the observed effects. Pentylenetetrazole (PTZ) produces generalized asynchronous clonic movements of the limbs, which are usually superseded by flexion and tonic extension of the fore and hindlimbs in laboratory animals. Although PTZ-induced seizures is similar to that observed in patients suffering from grand mal epilepsy, this model of epilepsy in mice is used to screen drugs of value in Petit mal epilepsy (Desmedt *et al.,* 1978; Kent and Webster, 1983; Franz, 1985). Although direct excitatory effects have not been excluded, a major action of pentylenetetrazole may be to reduce GABA-ergic inhibition, thereby enhancing CNS

excitability. Pentylenetetrazole reduces the impact of GABA on chloride ion conductance at concentrations that do not alter resting neuronal membrane conductance in the absence of GABA (Scholfield, 1982). A large body of electrophysiological and biochemical observations have suggested the involvement of dopaminergic mechanism in pentylenetetrazole-induced convulsions. Jones and Robert (1968); and Dadkar *et al.* (1979) observed that dopamine reduces the threshold of pentylenetetrazole convulsions in mice and pimozide (a specific dopamine receptor antagonist) protected experimental animals against pentylenetetrazole induced seizures (Amabeoku, 1989). Blockade of dopaminergic pathway may therefore be another possible mechanism by which the extract offered some protection against pentylenetetrazole induced seizure in mice in addition to others. In animals, prevention of pentylenetetrazole induced seizures by benzodiazepines is more prominent than their modification of the maximal electroshock seizure pattern (Theodare and Leonard, 1990). Clonazepam for instance, is unusually potent in antagonizing the effects of pentylenetetrazole, but it is almost without action on seizure induced by maximal electroshock (Swinyard and Castellion, 1966). It is therefore, not surprising that clonazepam (0.2mg/kg i.p.) protected the mice against all the episodes that were associated with pentylenetetrazole-induced seizures in this study. The extract had no protective effect against electroshock seizure in chicks. According to Swinyard (1972), the pattern of seizures induced by electroshock in laboratory animals is generally characterised by tonic extension of the fore and hindlimbs and it is similar to that observed in patients suffering from grandmal epilepsy.

Although the exact role of the biogenic amines in electrically induced seizures is not fully understood, a convincing body of biochemical evidence has accumulated implicating noradrenaline (NA), dopamine (DA), and serotonin (5-HT). Jobe et al., (1974) observed that DA and NA exert CNS effects that limit the spread of electroshock seizure discharge and consequently modulate the intensity of electroshock seizures. Increased levels of NA, DA and 5HT have been shown to have a protective effect against electroconvulsion in chicks and rats (Kilian and Frey, 1973; Osuide and Wambebe, 1979). Conversely, the depletion of NA and DA has been reported by Breese and Traylor (1971) to produce an enhanced electroconvulsive seizures. The extract lacked any protective effects against electroconvulsive seizure at the doses tested. Therefore it may not be valuable against electrically induced seizures.

We may therefore conclude, based on the data presented, that the use of *Ficus platyphylla* in traditional medicine in Nigeria and other West African countries is justifable scientifically. The stem bark contains some active principles whose total pharmacological activities correlate very well with those of clinically useful antipsychotic agents e.g. haloperidol. The crude extract is relatively safe (LD50 >2000 mg/kg i.p.). In addition, the extract possesses a strong analgesic and anti inflammatory activities which may be responsible for its use as analgesic. The plant extracts may also be valuable in convulsive disorders (particularly, Petitmal epilepsy). So far, our preliminary phytochemical study has revealed the presence of flavonoids, condensed tannins and saponins. Further investigation on the components so as to isolate the active ones will be most interesting.

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