Scientific Investigation of the anti-stress potential of selected herbal plants in heat-induced stressed rats.

A DISSERTION SUBMITTED TO THE DEPARTMENT OF PHARMACY, DAFFODIL INTERNATIONAL UNIVERSITY IN THE PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF PHARMACY.

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AThesispaper" **Scientific Investigation of stress and its's novel herbal remedies in Wistar Albino rats"**submittedtotheDepartment of Pharmacy, Faculty of Allied Health Science, Daffodil International University hasbeen accepted as satisfactory for partial fulfillment of the requirement for the degree of theBachelorofPharmacyand approved as to its styleandcontents.

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Acknowledgement

In order to satisfy the prerequisites for the Masterof Pharmacy degree, I must first express my sincere thankfulness to the Almighty God for providing me the opportunity to study this topic, the capacity to finish my project work, and ultimately the competence to summarize the thesis work's findings.

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Declaration

I hereby declare that the Thesis work title **“Scientific Investigation of stress and its’s novel herbal remedies in Wistar Albino rats”**requirement for the complete the Master of Pharmacy (M.pharm)programundertheFacultyofAlliedHealthScienceDaffodilInternationalUniversity.

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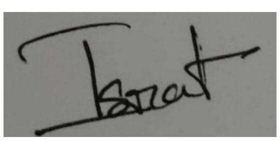

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Abstract

Stress is a state of mental strain for a specific person experiencing issues with their social and environmental well-being, which may result in a variety of illnesses. Stress is a factor in sickness and disease in 90% of cases. Body's natural functions and physical performance might be affected by stress. The study is designed to investigate the effects of herbs like rosemary, cinnamon and aloe vera in reducing stress level by determining the blood glucose level and serum cortisol level. And to find out the effects of anti-depressant and anxiolytic drugs on blood glucose and serum cortisol level. Cardiac puncture method was used for blood collection and spectrophotometric method was used to detect the blood glucose and cortisol level. The blood glucose level for herbal sample and standard groups were 6.1± 1.18 & 5.07± 0.208 mmol/L respectively where control group was 4.3 ± 0.321 mmol/L. Serum cortisol level 1.06± 0.23&0.92± 0.02 ug/dl for herbal and standard group drugs where 1.67± 0.499 ug/dl for control group. Morphological study of spleen was done to evaluate and compare the effectiveness of herbal and standard drugs against and the spleen mass of rats in the control group was 0.25 0.011 gm, while those in the standard group were 0.30 0.009 gm and those in the herbal combination group were 0.32 0.015 gm. The control group had a decrease in spleen size as a result of stress induction, whereas the other two groups saw substantial growth. Presents study indicates that herbal plants have the ability to reduce stress in normal range but further study is necessary to support theses statement.

Keywords: Stress, Herbal plant, Blood glucose, Serum Cortisol, Spleen, rats.

Table of Contents

Chapter-01

Introduction

1.1 Overview

Simply expressed, stress is the process through which an organism's adaptive capacity is strained by external demands, leading to behavioral and physiological changes that may enhance an organism's vulnerability to illness (1). Anxiety-inducing stimuli are referred to as stressors. Both the young and the old, as well as the wealthy and the poor, are susceptible to the negative consequences of stress. Daily living involves a great deal of stress. To exist in this world, one must be able to handle the inevitable tension that will come. Mental stress, for example, may increase a person's susceptibility to physical sickness. Environmental stress, psychological (emotional) stress, and biological stress [1] are three distinct concepts or viewpoints that may be applied to stress. The environmental stress method focuses on evaluating environmental situations or experiences that are objectively associated with high adaptation needs. According to the idea of psychological stress, individuals' perceptions of their resilience in the face of adversity are of the utmost significance. The biological stress perspective, which emphasizes the function that mental and physical stress play in the maintenance and control of the body's physiological systems, is the last but not least.

The relationship between stress and illness is intricate and complex. Everyone responds differently to stress. Something that makes one person ill would not necessarily make another one sick. A disease may arise only when certain triggers interact with a wide range of prior circumstances. Some individuals are more vulnerable to stress than others owing to a mix of genetic, coping, personality, and social support variables. We evaluate the severity of a scenario and examine our inventory for the necessary resources. If we feel the issue is significant yet lack the resources to handle it, we will suffer stress [2]. The manner in which we respond to numerous stimuli influences our vulnerability to disease and our general health.

It is essential to remember that not all stress is detrimental. When the body can adapt to stress and use it to combat fatigue or enhance performance, the experience is useful, healthy, and demanding. Hans Selye [3], an early researcher in the area of stress ology, invented the word "eustress." Adaptation to stress strengthens our coping systems, alerts us when we're not coping effectively, and suggests that a change in lifestyle is necessary to sustain health. This stress enhances performance, which is beneficial for athletes and public speakers alike. Stress impairs performance, accelerates systemic aging, and causes physical and mental disease. This anxious mental condition is known as distress. Reactivity, fogginess, loss of focus, and performance anxiety are all common stress-related outcomes that contribute to negative outcomes. The principle is shown in Figure 1.

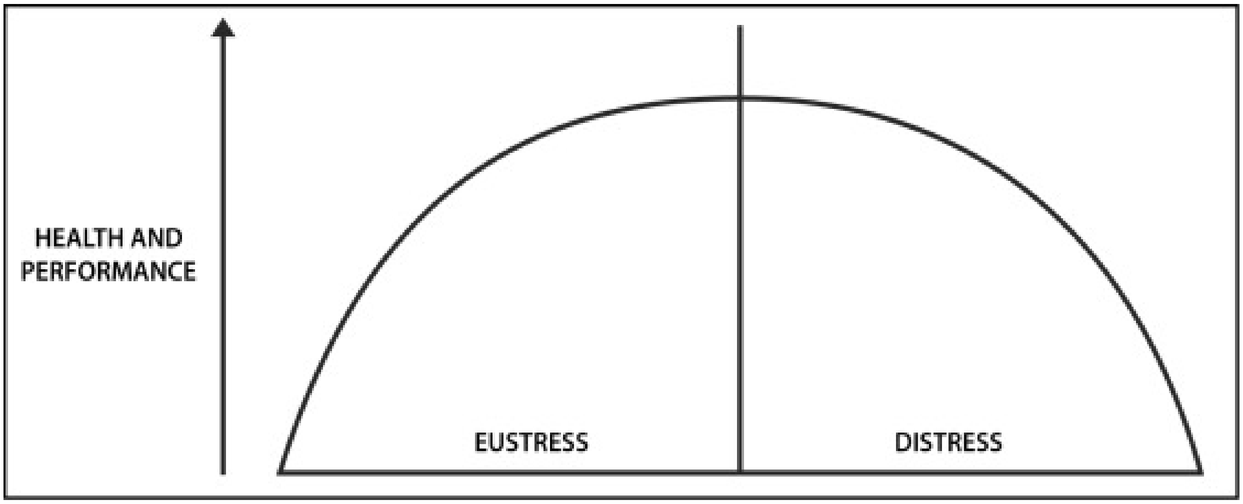

Figure 1 depicts eustress, the kind of stress that actually improves athletic performance.

The frequency and expense of stress-related disorders are growing, particularly in the setting of the workplace. In the 21st century, expressions such "worked to death," "drop death," and "work till you drop" have raised attention to labor-related fatalities. Countries with historically lengthy workweeks, such as Japan and China, are well aware of this problem and have their own words for death from overwork: karoshi and guolaosi, respectively. Both Japan and Korea see suicide as an occupational sickness covered by workers' compensation [4]. In the United Kingdom, the estimated prevalence of stress and stress-related diseases increased from 829 cases per 100,000 employees in 1990 to 1,700 cases per 100,000 in 2001/2002. This contributed to an estimated 13,4 million lost hour shifts owing to stress, anxiety, or despair. 1.3% of the working population suffers from stress, depression, or anxiety, according to the most recent HSE (Health and Safety Executive) evaluation of self-reported sickness rates [5]. According to estimates, between 80% and 90% of workplace accidents are caused by personal issues and the inability of employees to handle stress [6]. According to the European Agency for Safety and Health at Work [7], stress is the leading cause of employee absenteeism in around half of all occurrences.

Stress-related diseases are a leading source of morbidity and mortality, which is alarming. In the United States, cancer, cardiovascular disease, accidental deaths, respiratory illnesses, cirrhosis of the liver, and suicide are the top six causes of death. All of these conditions are significantly influenced by emotional stress. According to research conducted by the Meridian Stress Management Consultancy in the United Kingdom, around 180,000 British citizens die annually from stress-related disorders. According to the Centers for Disease Control and Prevention, about 75% of all healthcare visits in the United States are attributable to stress. This includes a broad range of health issues, including but not limited to aches and pains, sleep disorders, tiredness, accidents, and heart problems. The National Council on Compensation of Insurance and Occupational Health and Safety magazine [7] claim that up to 90 percent of all visits to primary care doctors are for stress-related issues.

1.2 Frequent causes of stress for students

Stressors might range from making a presentation in front of the class to taking all of your most challenging courses for a whole semester. Student anxiety may result from a number of circumstances, including:

Academic performance anxiety has been connected to a broad variety of stress symptoms, including anxiety, restlessness, changes in appetite, and even a change in one's overall temperament. According to Morehouse State University, adolescents have poor study habits and tend to cram for exams at the last minute. Workload and test anxiety are two main causes of stress for students. The majority of college students' anxiety is linked to their hard workload [8].

Money problems are something that every young adult must encounter. The majority of young people either cannot find job at all, or if they can, they are underpaid. They want to maintain a high standard of life and satisfy customer demand for autos, bicycles, and mobile phones. If they cannot meet the demand, they will face stress.

Connections - Your interactions with people may have a significant influence on your capacity to handle stress. Everyone desires friendships, whether they be casual or deep. If a person discovers that making friends is more difficult than anticipated, they may suffer a tremendous lot of stress.

The young of today are especially susceptible to work-career stress, a prevalent kind of chronic illness that may have severe effects on a person's productivity and health. Various factors, such as a harsh work atmosphere, a hostile coworker, or an unclear job future, may contribute to workplace stress. Students are concerned about slipping behind in today's competitive labor market [8].

Ineffective time management is a primary source of stress among high school and college students nowadays. It may be challenging to balance all of your obligations, including school, friends, and family. The difficulty rises when a part-time job is added [8].

1.3. The Influence of Oxidative stress on Cellular Mechanisms

The OS has a substantial effect on apoptosis, protopathic, proteasome dysfunction, mitochondrial dysfunction, glial cell activation, and neuroinflammation. Apoptosis, or programmed cell death, is a crucial physiological process for maintaining tissue homeostasis and avoiding an excess of cells. Apoptosis may be triggered from the outside, through death receptors, or from the inside, via the release of cytochrome c and caspases 8 and 9, and the consequent formation of the azotosome complex in the mitochondria. Both methods cause the release of caspase-3, which in turn activates the heterodimer of 40 kDa, caspase-activated DNase, nuclease (CAD) or DNA fragmentation factor 40, resulting in targeted DNA fragmentation and final apoptotic cell death. This is true of seizure-induced neuronal death, as shown by animal experiments. Apoptotic cells may be identified by changes in biochemistry and morphology, such as chromatin condensation, cell shrinkage, and internucleosomal DNA fragmentation [9].

1.4. Association of Oxidative Stress and Nutritional Status in Lung Disease

Respiratory illnesses, such as asthma and chronic obstructive pulmonary disease (COPD), have been identified as significant global health problems due to increased incidence and mortality rates. Increasing environmental exposure to air pollution and cigarette smoke is a crucial factor in the development of obstructive stomatitis in COPD. By causing direct harm to alveoli and lung connective tissue, oxidant toxicity accelerates the pathogenesis of COPD. Activation of inflammatory cells, which create even more ROS in the lungs, is an additional consequence of excessive ROS generation. This mechanism initiates the vicious cycle of chronic inflammation and obstructive lung illness found in COPD. OS has been linked to the pathophysiology of asthma. Uncertainty exists as to whether high OS in asthma is a cause of the disease or a consequence of inflammation, however it is thought that OS plays a vital role in the development of asthma. By activating transcription factors such as nuclear factor-kappa B (NF-kB), mitogen-activated protein kinase (MAPK), and activator protein-1 (AP-1), OS exacerbates airway inflammation in bronchial asthma. It also increases airway hyperreactivity and mucus production, two features associated with severe asthma. Increased endogenous ROS production is a consequence of both the respiratory system damage produced by OS and the diminished antioxidant defenses resulting from this damage [10].

1.5. Role of Pro-Oxygenants in Oxidative Stress

Both endogenous and exogenous pro-oxidants have been found as important contributors to oxidative stress. Fruits and vegetables, which are rich in polyphenols, are believed to be potent antioxidants. This information motivates us to include these ingredients more often into our normal meals. However, the persistence of chronic health problems and neurodegenerative diseases shows that there may be other processes associated with oxidative stress beyond antioxidants, which were later identified as pro-oxidants. Thus, pro-oxidants consume any endobiotic or xenobiotic species, which either produces oxidative stress by producing reactive oxygen and nitrogen species (ROS/RNS) or impedes the antioxidant system's capacity to fulfill its function in cells and tissues. Pro-oxidants may be further classified as either exogenous (from the outside) or endogenous (from inside) [11]. Endogenous pro-oxidants may be broken down into stress, ion flux, climate, environmental pollution, drug metabolites, and so on. Exogenous pro-oxidants can be broken down into pathogens, drugs, toxicants, dietary components, and so on.

1.6.Neurodegenerative Disorders and Oxidative Stress

A single injured cell initiates degenerative processes such as mitochondrial failure, neuroinflammation, apoptosis, and tissue necrosis. oxidative stress promotes homeostatic instability, which is shared by Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) (ALS). Injuries such as stroke, spinal cord injury (SCI), peripheral nerve damage (PNI), etc., may induce neurodegenerative diseases. Neurodegenerative disorders [12] are connected to oxidative stress, inadequate antioxidant defense, and mitochondrial dysfunction.

1.6.1 Alzheimer's Disease and Oxidative Stress

Patients with Alzheimer's disease, the most prevalent type of neurodegenerative illness, see a deterioration in their ability to do even the most fundamental activities, which has a significant influence on their quality of life.As seen in the following graphic, stress may cause Alzheimer's disease.

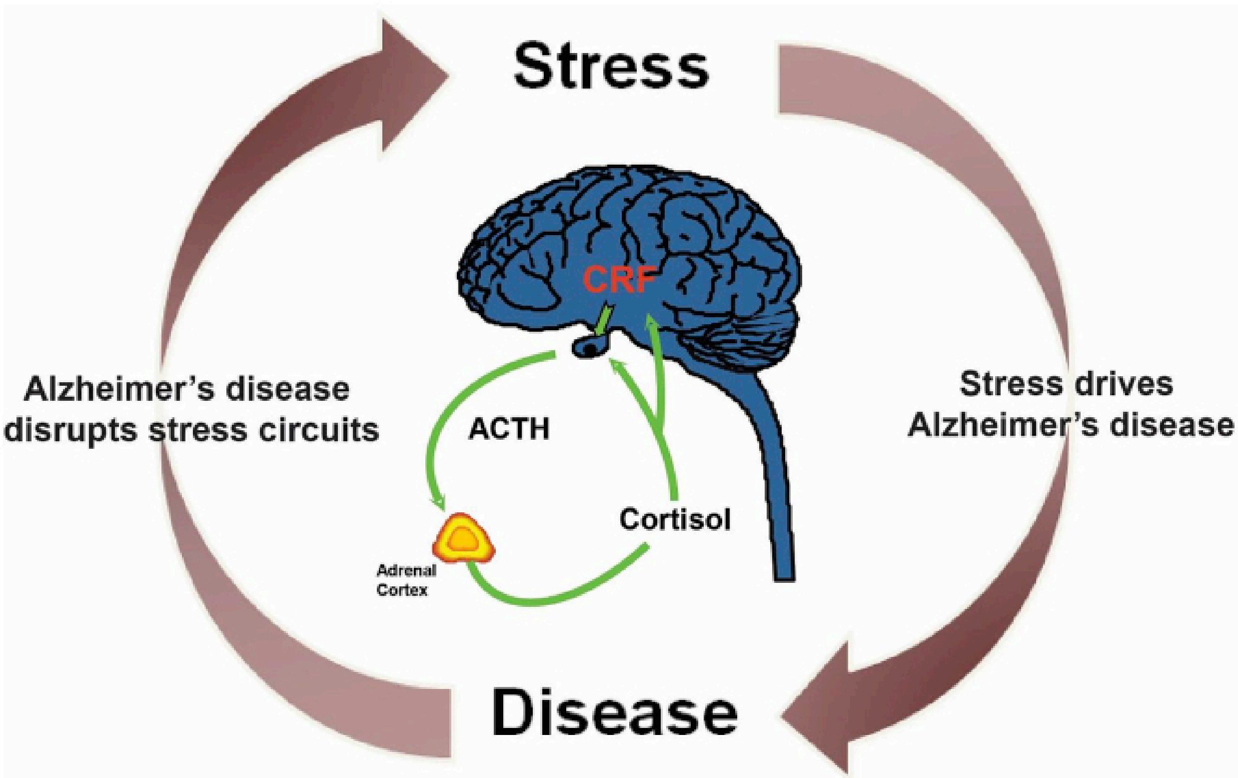

Figure: Alzheimer disease and stress

Alzheimer's disease (AD) is characterized by the formation of amyloid beta (A) plaques outside of cells and tau neurofibrillary tangles inside of cells, which are the illness's key pathological hallmarks (NFT). Ca2+ overload in the cytosol might be the result of A plaques depleting Ca2+ reserves in the endoplasmic reticulum (ER). When cytosolic Ca2+ levels increase, endogenous GSH levels decrease and reactive oxygen species (ROS) may accumulate to hazardous levels within the cell. Overproduction of reactive oxygen species (ROS) is anticipated to have a substantial role in the accumulation and deposition of A in Alzheimer's disease, and ROS-induced oxidative stress is consequently emerging as a crucial component in the pathogenesis of Alzheimer's disease. Possible effects of mitochondrial dysfunction include excitotoxicity, disturbance of Ca2+ homeostasis, reduced ATP production, and ROS dysregulation. All of these alterations may contribute to the development of AD. Overactivation of N-methyl-D-aspartate-type glutamate receptors may contribute to AD patients' severe OS (NMDARs). Activation of NMDARs has been associated with neurotoxic levels of reactive oxygen and nitrogen species (ROS) and Ca2+ influx through enhanced cell permeability (RNS). Possible mediators of the JNK/stress-activated protein kinase pathways include reactive oxygen species (ROS). These cascades have been connected to both the hyperphosphorylation of tau proteins and A-induced cell death. A proteins may also directly induce free radical generation by activating NADPH oxidase. Enhanced reactive oxygen species (ROS) generation in response to A modifies cellular signaling pathways and induces tau hyperphosphorylation through activation of p38 mitogen-activated protein kinase (MAPK). The formation of intracellular NFTs may be initiated by an abnormal accumulation of hyperphosphorylated tau proteins [13].

1.7 Pollutant oxygen release and the progression of Parkinson's disease (PD)

Parkinson's disease (PD), the second most prevalent neurodegenerative condition, is characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta. The prevalence of Parkinson's disease increases with age, affecting 1% to 2% of individuals over 65 and 4% to 5% of those over 85. An increase of reactive oxygen species (ROS) or other free radicals has been associated with dopaminergic neuron degeneration. Both mitochondrial dysfunction and inflammation have been linked to excessive ROS generation. Redox equilibrium is required for neuron survival and proper function of redox-sensitive signaling proteins in neuron cells. ROS are principally produced by mitochondria in neurons and glial cells in the brain. Neuroinflammation, dopamine breakdown, mitochondrial malfunction, aging, GSH depletion, and higher iron or Ca2+ levels all contribute to the increased formation of free radicals seen in Parkinson's disease. Furthermore, environmental factors such as pesticides, neurotoxins, and dopamine may aggravate ROS accumulation in PD. It is evident that this is the case due to the high association between pesticide exposure and an elevated risk of PD. Researchers have shown that ROS are essential to the demise of dopaminergic neurons. Researchers have discovered a link between neuromelanin and the decline of dopaminergic neurons. This makes logical, since neurons with a high melanin content are more susceptible to injury. Excessive production of reactive oxygen species (ROS) seems to contribute to the formation of neuromelanin [14–17].

1.8 Systemic Oxidative Stress Evaluation

Numerous surrogate markers for oxidative stress or antioxidant activity, such as circulating lipid peroxides, glutathione (GSH), and vitamins C and E, have been measured in peripheral blood because oxidative stress may be a shared pathophysiological mechanism underlying multiple neurodegenerative disorders. Individuals with AD have reduced amounts of vitamin A, C, and E in the peripheral, as well as poorer superoxide dismutase and glutathione peroxidase activities. Plasma levels of glutathione (GSH) have been hypothesized as a primary predictor of cognitive abilities in Alzheimer's disease (AD) patients, suggesting a correlation between lower plasma levels of GSH and more severe cognitive impairment. Patients with PD would have altered SOD activity in erythrocyte, however results have been inconsistent. An increase in SOD activity may play a role in guarding against the increased production of O2 associated with neurodegenerative diseases [18].

1.9 Association between stress and cancer

Due of its probable relation to breast cancer, stress has been widely examined. Some study has connected recent grief to early death, particularly from cancer. According to a tiny number of studies of women with breast cancer, those who had had horrific life events and losses in the years preceding up to their diagnosis had a considerably increased chance of developing the disease. However, the majority of cancers grow over a period of years and are not identified until they have spread throughout the body. Therefore, this event offers evidence against the theory that suffering the death of a loved one may cause cancer. However, these immune system modifications have not been related to an increased risk of cancer in any research. Changes in the immune system caused by stress have not been conclusively linked to cancer. To assess if mental stress contributes to the malignant transformation of normal cells, more research is necessary. Active research [19] focuses on reducing stress in cancer patients, enhancing immunological function, and perhaps prolonging survival time.

1.10. Neurological Effects of Oxidative Stress

The term reactive oxygen species (ROS) refers to a collection of free radicals that do not strictly conform to the concept of a free radical. This category contains singlet oxygen, superoxide anion, hydroxyl free radical, hydrogen peroxide, and hypochlorous acid. As signaling molecules involved in cell proliferation and death, low levels of reactive oxygen species (ROS) are important for appropriate neuronal development and function in the brain (CNS). In appropriate numbers, they contribute to the battle against infections. However, when their numbers become excessive, they injure cells and cause DNA mutations that eventually result in cell death. Reactive oxygen species are byproducts of oxidation that drive subsequent oxidative chain reactions (ROS). This chain reaction is dubbed "autoxidation" because it occurs spontaneously and under benign environmental conditions. Peroxidation occurs when peroxidases are formed as byproducts. During the oxidative chain reaction, reactive oxygen species (ROS) accumulate owing to an imbalance between their production and destruction. This kind of imbalance is known as oxidative stress.

The damage to the brain generated by oxidative stress has a dramatic influence on the actions of the central nervous system. The brain is especially sensitive to oxidative stress due to its high oxygen needs, high polyunsaturated fatty acid (PUFA) content in nerve cell membranes, and accumulation of transition metals [51]. The high metabolic rate of the brain enables it to use around 20% of the total energy needed by the human body. The production of this fuel is the responsibility of the mitochondria of brain cells. Seventy to eighty percent of the brain's energy is consumed by neurons, while the remainder is used by glial cells [52]. Mitochondria create around 80% of reactive oxygen species (ROS) in brain cells, which assists in appropriate cellular functioning. Due to electron leakage at four complexes (I-IV), the ROS threshold is surpassed, resulting in molecular stress. DNA oxidation, lipid peroxidation, and protein oxidation all occur when ROS levels grow. In addition, the brain has an abundance of polyunsaturated fatty acids, particularly docosahexaenoic acid, which promotes lipid peroxidation. The decomposition of lipids by free radicals is known as lipid peroxidation. When free radicals attack PUFA in the membrane of a brain cell, highly active aldehydes are generated, which subsequently (a) stiffen the membrane, (b) inhibit sodium pump function, (c) alter membrane permeability, and (d) injure the cell. The accumulation of transition metals is the principal cause of oxidative stress in the central nervous system (CNS). Iron, copper, and zinc are all transition metals that play crucial roles in biological processes such as cell division, DNA synthesis, and neurotransmitter creation. In addition, it is well established that iron and copper serve as catalysts for ROS production in cells. These metals produce an increase in reactive oxygen species (ROS), which leads to lipid peroxidation, oxidative stress, and cell damage.

1.11Stress Management

1.11.1 Alzheimer's disease treatment

Cholinesterase inhibition

The cholinergic hypothesis of Alzheimer's disease postulates that memory loss and deterioration of other cognitive and noncognitive processes, such as neuropsychiatric symptoms, are caused by damage to cholinergic systems in the basal forebrain during the onset of the disease. As a technique of enhancing cholinergic transmission, the use of CIs to postpone acetylcholine breakdown across synaptic clefts has been suggested. Three CIs are now licensed for the treatment of mild to severe Alzheimer's disease: donepezil (Pfizer, New York, NY, USA), rivastigmine (Novartis, Basel, Switzerland), and galantamine (Janssen, Beerse, Belgium) [27, 28].

In opposition to N-methyl-D-aspartate

For more severe forms of Alzheimer's disease, memantine may be used as an adjuvant to other therapies (Lundbeck, Valby, Denmark). As a noncompetitive NMDA antagonist with modest affinity, this medication is intended to protect neurons from excitotoxicity. A systematic evaluation of double-blind, parallel-group, RCT studies revealed that after six months of treatment, memantine improved cognition, ADL, and behavior in moderate to severe AD patients. Another meta-analysis of six randomized controlled trials (RCTs) reveals that memantine may improve behavioral and psychological dementia symptoms. Studies on memantine most often identified dizziness, headaches, and disorientation as side effects. Certain patients may get irate [29–31].

Chemotherapy and/or antibacterial drugs

In RCT investigations on parallel groups evaluating cognitive function, language, ADL, behavioral, and general status of individuals with moderate to severe AD, the combination treatment of memantine and donepezil shown considerable gains over placebo in comparison to the placebo group. Despite [32, 33], there is little evidence that treatment benefits moderate to severe AD patients.

1.11.2 Method Two: Depression Treatment

ANTIDEPRESSANT PRODUCTS •Tricyclic and tetracyclic antidepressants (TCAs)

Clomipramine is more effective than nonselective serotonin reuptake inhibitors (NSRIs) such as amitriptyline, doxepin, and amoxapine, although desipramine is more effective than amitriptyline (NRI)

Serotonin reuptake inhibitors are medications that specifically block serotonin's actions (SSRIs)

These kinds of medications include citalopram, escitalopram, fluoxetine (also NRI), fluvoxamine (also weak NRI and melatonin agonist), paroxetine (also NRI>>DaRI), and sertraline (also DaRI>>NRI).

Selected inhibitors of serotonin and noradrenaline reuptake (SNRIs)

Duloxetine, Venlafaxine, and Milnacipran

An antagonist of the 2-adrenergic and serotonin 5-HT2A receptors

Mirtazapine and maniaserine

Serotonin (5-hydroxytryptamine) 2 receptor antagonists

Trazodone and nefazodone

Reuptake inhibitor of norepinephrine

Reboxetine

Drugs that prevent the reabsorption of dopamine into the brain are a popular therapy option.

Methylphenidate, Bupropion (also a moderate NI), and Naltrexone are examples of NIs.

Antidepressants that are atypical; monoamine oxidase inhibitors (MAOIs)

Reversible and selective inhibitors of monoamine oxidase (MAOI-A; moclobemide, toloxatone) MAOI-B are irreversible, nonselective monoamine oxidase inhibitors (selegiline)

Antagonist of 5hydroxytryptamine 2 (HT2) receptors and agonist of melatonin receptors (MT1/2).

Here we have agomelatine [34].

1.12 Herbs used to treat stress-related disorders

The most prevalent forms of emotional suffering in contemporary civilization are sadness, anxiety, and sleeplessness. Depression is one of the most common mental disorders, and it has far-reaching effects on both people and societies. The World Health Organization (WHO) predicts that by the year 2020 [35], major depressive disorders (MDD) would be the second most prevalent health issue in the world. The 2010 Global Burden of Disease Study [36] found that major depressive disorder (MDD) was the second leading cause of disability globally. In addition, the risk of ischemic heart disease was considerably increased. Since the 1960s, "major depression" has been diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders [37] criteria as depression.

Anxiety is a frequent symptom of several physical and mental health conditions. In reality, it is a typical human emotion that serves as a defensive reaction to dangers (akin to healthy fear) and a coping mechanism for adjusting to environmental change [38]. One in five individuals worldwide will have clinically diagnosable anxiety at some point [39]. In the discipline of psychopharmacology, the research of anxiety disorders has increased significantly during the last decade. Many individuals with anxiety also have difficulty sleeping. Subjectively, the most prevalent sleep disturbance is the sensation of being unable to fall asleep or remain asleep, or of experiencing sleep that is not restorative and/or is of poor quality and/or length [40]. Insomnia, the most widespread health problem in the United States, may result in serious medical disorders [41]. There are significant daytime consequences for the 9-15% of the world's population that suffers from insomnia [42]. Consequently, sadness, anxiety, and sleeplessness are all instances of comorbid psychiatric illnesses that compound mental health conditions. Severe sadness, sleeplessness, and anxiety disorders all negatively impact the immunological and cardiovascular systems [43]. In addition to diminishing people's feeling of well-being and quality of life, these mental health concerns have detrimental effects on their daily lives and their capacity to maintain profitable employment. According to our current understanding, the number of persons having mental health issues is rising quickly over the world [44]. Therefore, research into more effective therapies is necessary.

1.12.1 Herbal Antidepressants Relate to Depression

Common mental illness that seriously hinders a person's quality of life is major depressive disorder. The majority of synthetic antidepressants have significant downsides, including a lack of alternatives, severe side effects, expensive prices, and the possibility of relapse. Herbal remedies are growing in popularity as individuals seek multi-target antidepressants with minimal adverse effects. The complex etiology of depression is likely related to the observation that a variety of mental disorders share distinct metabolic abnormalities [44]. Decreased levels of 5-hydroxytryptamine (5-HT), norepinephrine (NE), and dopamine (DA) are examples of the damage to monoamine transmission networks that underlies depression [45, 46].

On the basis of this principle, many antidepressants, some of which are herbal, have been produced; they function by preventing the reuptake of certain neurotransmitters by the brain. Numerous medicines operate through this mechanism [47, 48]. Some herbal medications have antidepressant effects through blocking monoamine oxidases or by increasing serotonin receptor sensitivity, whilst others do not. It is commonly known that ginseng, a plant used for thousands of years to enhance mental and physical health in traditional Chinese medicine, has a long history of use in the west. In rodent models, 20(S)-protopanaxadiol, a chemical derived from ginseng, exhibited potential antidepressant qualities by increasing NE and 5-HT levels in the brains of OB

rats. Inhibition of monoamine reuptake may contribute to the efficacy of this medication [49]. Peony, often referred to as the root section of the plant Paeonia lactiflora Pall (Ranunculaceaeprocessed), is a key component in several traditional Chinese medicine remedies for the treatment of depression [50,51]. The ethanol extract and total glycoside fraction of peony (TGP) exhibit antidepressant effects in rats under normal physiological conditions, according to previous investigations [52, 53]. Subsequent study has shown that TGP alleviates depressive symptoms brought on by sustained unexpected stress [54], indicating that the antidepressant-like effect of TGP is mediated through inhibition of monoamine oxidases and the reduction of oxidative stress in mouse brain. At least in part, anxiety, sadness, and the actions of tranquilizers and mood stabilizers may be attributed to 5-HT1A receptors [55]. Ji-Hyun Kim discovered that acute administration with the methylene chloride fraction of Albizia julibrissin (MCAJ) significantly decreased immobility time in forced swimming experiments, suggesting antidepressant potential [56]. Albizia julibrissin, sometimes known as the mimosa tree, is a popular ornamental in Asia. Temporarily ameliorate symptoms using pindolol, an antagonist of the 5-HT1A/1B receptor, or WAY-100635, an antagonist of the 5-HT1A receptor. It is commonly accepted that the hypothalamic-pituitary-adrenal (HPA) axis is engaged whenever the brain undergoes acute or chronic stress. PVN neurons create and release corticotropin-releasing factor (CRF), which encourages the anterior pituitary to secrete adrenocorticotropin (ACTH), which induces the adrenal cortex to make and secrete glucocorticoids (cortisol in humans and cortisol in rats) [57]. Current theories imply that high blood cortisol and accelerated CRF transmission in some brain areas are the consequence of excessive activation of the HPA axis, and hence substantially contribute to depressive symptoms [58].

1.11.2. Medicinal plants that alleviate anxiety

Several mental disorders, including GAD, PAD, PTSD, OCD, and phobias, share the symptom of anxiety. How precisely anxiety disorders operate remains a mystery. Recent research indicates that anomalies in serotonergic, noradrenergic, glutamatergic, and GABAergic transmission may be the neurobiological cause of anxiety [61]. These pathways are used by several medications, including benzodiazepines, SSRIs, SNRIs, and others, to treat anxiety disorders [62]. Long-term use of these medications always results in adverse consequences, such as tolerance or dependence. Numerous individuals are interested in the efficacy of plant extracts and drugs obtained from natural sources in treating anxiety disorders. The Kampo formula Kamishoyosan, which comprises of eleven herbs including Gardeniae fructus, may treat menopausal psychosis. Research indicates that Gardeniae fructus and geniposide in Kamishoyosan are at least partially responsible for the anxiolytic effects [63], since dose-dependent oral administration of the extract or the principal component (geniposide) prolonged the length of social interactions.

G. Ginkgo biloba leaf extracts (EGb) are often utilized for their ability to treat mental symptoms. When there is an excess of EGb [64], tritiated neurotransmitters (such as NE, DA, and 5-HT) cannot enter synaptosome-rich areas of the rat brain. Anxiety is a typical symptom of mental illness, but EGb 761, which reduces the development of dementia, may help patients suffering from these disorders feel better. The precise mechanism by which EGb 761 exerts its anti-anxiety properties remains unknown. Multiple studies [65–67] have connected high CRH levels and hyperactivity of the HPA axis to the development of depression and anxiety disorders in humans.

Chapter-02

Plant Profile

2.1 Rosemary

Scientific name:*Salvia rosmarinus*

Scientific Classification

Kingdom:	**Plantae**
Clade:	Tracheophytes
Clade:	Angiosperms
Clade:	Eudicots
Clade:	Asterids
Order:	Lamiales
Family:	Lamiaceae
Genus:	Salvia
Species:	S. Rosmarinus

Pharmacological Uses of Rosemary

Significant antibacterial, anti-inflammatory, antioxidant, anti-tumorigenic, anti-apoptotic, anti-nociceptive, and neuroprotective effects are present in rosemary. It also demonstrates significant therapeutic benefits on mood, memory, learning, pain, anxiety, and sleep [68].

Figure: Rosemary

2.2 Aloe vera

Scientific name: Aloe vera

Scientific Classification

Kingdom:	**Plantae**
***Clade*:**	Tracheophytes
***Clade*:**	Angiosperms
***Clade*:**	Monocots
Order:	Asparagales
Family:	Asphodelaceae
Subfamily:	Asphodeloideae

Genus:	Aloe
Species:	A. vera

Pharmacological Uses of Aloe vera

This medicinal herb has traditionally been used to treat skin conditions (burns, wounds, and anti-inflammatory processes).

Figure: Aloe vera

Aloe vera has also demonstrated various medicinal qualities, such as anticancer, antioxidant, antidiabetic, and antihyperlipidemic [69].

2.3 Cinnamon

Scientific Name:*Cinnamomum verum*

Scientific Classification

Kingdom:	**Plantae**

***Clade*:**	Tracheophytes
***Clade*:**	Angiosperms
***Clade*:**	Magnoliids
Order:	Laurales
Family:	Lauraceae
Genus:	Cinnamomum
Species:	***C. verum***

Pharmacological uses of Cinnamon

Due to its capacity to freshen the mouth and eliminate bad breath, cinnamon is used as a spice and flavoring ingredient as well as to flavor chewing gum [70]. Additionally, cinnamon can enhance colon health, lowering the risk of colon cancer [71].

Figure: Cinnamon

As a coagulant, cinnamon stops bleeding [72]. Additionally, cinnamon promotes tissue regeneration and improves uterine blood flow [73]. Although this plant is mostly used as a spice, its essential oils and other components also possess significant antibacterial, antifungal, antioxidant, and antidiabetic properties [74].

Chapter-03

Literature Review

3.1 GhasemzadehRahbardar M, Hosseinzadeh H. Therapeutic effects of rosemary (Rosmarinus officinalis L.) and its active components on nervous system illnesses. Iran J Basic Med Sci. 2020 Sep;23(9):1100-1112.

The evergreen bushy plant known as rosemary (Rosmarinus officinalis L.) is endemic to the sub-Himalayas and the Mediterranean. Traditional medicine practitioners have prescribed it for a variety of conditions, including intercostal neuralgia, headache, migraine, insomnia, irritability, and depression. It has mild analgesic and antispasmodic effects as well. The neuropharmacological effects of rosemary have been the topic of a large number of investigations. Rosemary has powerful properties that help fight against infection, inflammation, cancer, apoptosis, pain, and nerve damage. Positive effects on a variety of mental health indicators, including disposition, memory, learning, pain, anxiety, and sleep, have been shown. This study aims to remind us of rosemary's therapeutic potential by reviewing the neuropharmacological effects of its numerous extracts and active constituents on illnesses of the nervous system, their related processes, and their preclinical application. The data came from a search of English-language publications in PubMed, Scopus, Google Scholar, and the Web of Science. Rosemary (Rosmarinus officinalis), depression, memory, Alzheimer's disease, epilepsy, addiction, neuropathic pain, and disorders were some of the terms utilized in the search. There were a number of helpful books, abstracts, and articles provided. There was no consideration given to the passage of time. The scope of this investigation included both in vitro and in vivo studies. This study lends credence to previous findings that rosemary is effective against inflammation, relieves pain, calms nerves, and boosts memory. Further, it provides a new angle for studying isolated ingredients, such as carnosic acid, rosmarinic acid, and essential oils, in quest of exquisite therapies and in assistance of the creation of medications with fewer side effects that may assist in the treatment of nervous system problems [68].

3.2 Liu L, Liu C, Wang Y, Wang P, Li Y, Li B. Herbal Medicine for Anxiety, Depression and Insomnia. CurrNeuropharmacol. 2015;13(4):481-93.

It's quite common for people to struggle with many mental health issues at once, including depression, anxiety, and insomnia. These are all very common mental illnesses that have impacted many individuals from different parts of the globe. Herbal remedies are widely utilized for the treatment of mental disorders, both as single herbs and in combination. Many people are turning to herbal remedies as an alternative to conventional medication because of the negative affects they have experienced from using it. In recent years, there has been a lot of interest in the field of herbal psychopharmacology. The research found that many herbal remedies for depression, anxiety, and insomnia act by modulating the hypothalamic-pituitary-adrenal axis (HPA), monoamine reuptake, neuroreceptor binding, and channel transporter function. Nonetheless, there has yet to be a thorough investigation on the efficacy of herbal therapy in treating mood disorders and insomnia. This review provides useful information for the practice of herbal medicine by better defining the mechanisms of action of diverse herbal medications.

3.3 Sánchez M, González-Burgos E, Iglesias I, Gómez-Serranillos MP. Pharmacological Update Properties of Aloe Vera and its Major Active Constituents. Molecules. 2020 Mar 13;25(6):1324.

Aloe vera has been used traditionally to treat gastrointestinal problems and skin injuries due to its anti-inflammatory, antibacterial, and wound-healing properties (burns, wounds, insect bites, and eczemas). The purpose of studying this medicinal plant has been to verify its traditional uses, deduce its mechanism of action, and identify its active compounds. Aloe-emodin, acemannan, aloin, aloesin, and emodin are among the most studied active components. The possible new actions of aloe vera and its active components have also been investigated. Recent in vitro, in vivo, and clinical pharmacology studies that have been published in English during the last six years are summarized in this review (2014–2019). According to the most recent analysis of pharmacological data, much of the research has been on the effects of the compound on cancer, the skin, and the digestive system, as well as the compound's antibacterial properties. The most up-to-date methods of study include in vitro and in vivo tests. In contrast to Aloe vera, which has been the focus of clinical investigations, isolated compounds have not. Researching the therapeutic effects of key metabolites across a spectrum of illnesses and human conditions would be fascinating. In light of these encouraging preliminary studies, further clinical trials are needed to further investigate the therapeutic application of aloe vera and its principal components, especially in the treatment of diabetes, cancer, and bone protection [69].

3.4 PasupuletiVisweswara Rao, Siew Hua Gan, "Cinnamon: A Multifaceted Medicinal Plant", Evidence-Based Complementary and Alternative Medicine, vol. 2014, Article ID 642942, 12 pages, 2014.

Cinnamon, a perennial tree used in tropical medicine, is a member of the Lauraceae family (Cinnamomum zeylanicum and Cinnamon cassia). It's no exaggeration to say that cinnamon is one of the most important spices in common use. Besides the essential oils, cinnamon also contains compounds like cinnamaldehyde, cinnamic acid, and cinnamate. In addition to its antioxidant, anti-inflammatory, antidiabetic, antibacterial, anticancer, lipid-lowering, and cardiovascular-disease-lowering properties, cinnamon has been shown to have effects against neurological conditions like Parkinson's and Alzheimer's disease. For an example of cinnamon's pharmacological potential and practical application, see this review [74].

Chapter- 04

Purpose of the Study

4. Purpose of the study

Stress may occasionally be a useful tool for increasing vitality and focus. But most of the time, stress is a detrimental influence in a person's life that leads to a variety of undesirable outcomes. Since almost everyone experiences stress, everyone may gain from understanding the condition. One can start to combat the effects of stress by being aware of how pervasive and detrimental it is.

- The main goal of the study was to find out the potential effects of herbal plants in controlling stress induced disease.

Chapter-05

Materials & Method

5. Materials & Method

5.1 Drug selection

This research evaluated the doses of the most widely used antidepressants and anxiolytics. For the investigation, about 100 prescriptions from patients at various hospitals in Dhaka, the capital of Bangladesh, were collected. The most often prescribed antidepressants and anxiolytics drug used throughout the animal study was used to compile, review, and finalize these prescriptions.

5.2 Herbal Plant powder collection

Herbal plant powder of Cinnamon, rosemary and Aloe vera were collected from super shop.

5.3 Suspension preparation of herbal plants

Cinnamon, rosemary and Aloe vera powder were mixed together at a dose 500mg/kg and distilled water was used to make the suspension.

5.4 Experimental design

Wister Albino rats were obtained for this research from the Jahangirnagar University Lab. The trials used male albino rats who were five months old and weighed between 160 and 180 g. The rats were housed in colony cages in the department's temperature-controlled (25–30 °C) animal room for 5 days prior to the experiment. To keep things clean, the bedding was changed every day.

For stress induction heat method was used at 39℃ for 10 minutes.

For the study the rats were divided into four groups and each group consist of n=3 rats. The three groups were:

- Control Group
- Group-2 (Standard drug)
- Group- 1 (Sample / Herbal combination)

5.5 Medication and Herbal combination

Table:Medication &Herbal combinationperformed throughout the study

Group	Medication & Herbal combination	Duration
Control Group	Normal water	21 days
Standard drug Group-2	Bromazepam Amitriptyline + Chlordiazepoxide	
Group-1 (Herbal combination)	Cinnamon + Aloe vera + Rosemary powder at a dose 0.5 g/ kg body weight.	

5.6 Blood collection

The investigational medications and samples were successfully administered to the rats for 21 days before they were killed and blood samples were collected. The cardiac puncture procedure was used to collect a blood sample of 2–3 ml. After centrifuging it, the serum was extracted from the blood and preserved for subsequent study.

5.7 Biochemical test

The investigation included two biochemical tests. The first is blood glucose, while the second is the Serum cortisol level. Both tests were carried out with spectrophotometry on a Backman Coulter AU-480 (model) machine.

5.8 Morphological Study

Morphological study of spleen was investigated to confirmed that herbal plants effective against stress.

Chapter-06

Result & Discussion

6.1 Biochemical Test

6.1.1 **Effects of Herbal sample, Standard drugs on blood glucose**

Table: Effects of Herbal sample, Standard drugs on blood glucose

Group Name	Medication & Herbal combination	Blood glucose (mmol/L)	Normal Range (mmol/L)
Control group	Water	4.3 ± 0.321	3.95-5.65
Group-1(Herbal combination)	Cinnamon + Aloe vera + Rosemary powder at a dose 0.5 g/ kg body weight.	6.1± 1.18	
Group-2 (Anti-depressant & Anxiolytic)	Bromazepam Amitriptyline + Chlordiazepoxide	5.07± 0.208	

Data were expressed as mean ± SEM (Standard Error Mean) where n= 3 for single group.

According to the aforementioned table, the control group's blood glucose level was 4.3 ±0.321 mmol/l, which means that no changes occurred in the level since it was within the normal range.

On the other hand, animals in the control group had glucose levels that were within the usual range (5.07± 0.208 level mmol/l), demonstrating that they are quite adept at minimizing stress. However, the blood glucose level of the herbal sample group was 6.1±1.18 mmol/l, which was somewhat beyond the normal range of glucose.

6.1.2 Effects of Herbal sample, Standard drugs on serum cortisol

Table: Effects of Herbal sample, Standard drugs on serum cortisol

Group Name	Medication & Herbal combination	Serum cortisol (ug/ dl)
Control group	Water	1.67± 0.499

Group-1(Herbal combination)	Cinnamon + Aloe vera + Rosemary powder at a dose 0.5 g/ kg body weight.	1.06± 0.23
Group-2 (Anti-depressant & Anxiolytic)	Bromazepam Amitriptyline + Chlordiazepoxide	0.92± 0.02

Data were expressed as mean ± SEM (Standard Error Mean) where n= 3 for single group.

The above table expressed that the serum cortisol level for control group was 1.67± 0.499ug/ml which indicates that stress was induced in the control group animals and it also support that stress condition can be formed in animals in high temperature.

On the other hand, in standard group animals the cortisol level was 1.06± 0.23IU/ml which manifested that they are highly capable in reducing stress and the level was within the normal range. A great finding was observed in herbal sample group where serum serum cortisol level 0.92± 0.02was ug/ml, so this result dictates that herbal plants has the capacity in lowering stress in animals.

6.2 Morphological Study

In morphological study of spleen, it was found that the control group spleen size was smaller than group 2 and 3 which indicates herbal plants and standard drugs are capable in controlling stress.

Table 6.2.1 Comparison of spleen size among experimental animals

Group Name	Medication & Herbal combination	Spleen weight (gm)	Spleen size (mm)
Control group	Water	0.25± 0.011	2.8±0.072
Group-1(Herbal combination)	Cinnamon + Aloe vera + Rosemary powder at a dose 0.5 g/ kg body weight.	0.32± 0.015	3.0±0.090
Group-2 (Anti-depressant & Anxiolytic)	Bromazepam Amitriptyline + Chlordiazepoxide	0.30± 0.009	3.2±0.981

Data were expressed as mean ± SEM (Standard Error Mean) where n= 3 for single group

From what we can gather from the table above, the rat's spleen in the control group weighed 0.25± 0.011 gm, while those in the standard group weighed 0.30± 0.009 gm, and those in the herbal combination weighed 0.32± 0.015 gm. The control group had a decrease in spleen size as a result of stress induction, whereas the spleen size of the experimental and comparison groups was considerably higher. And the size of the spleen for control group, standard group and herbal sample group 2.8±0.072, 3.2±0.981 & 3.0±0.090 mm respectively.

Figure: Spleen of different group rats

Chapter-07

Conclusion

7. Conclusion

It is concerning because stress-related illnesses are a major cause of morbidity and death.Through the study it was found that the blood glucose level of the herbal sample group was 6.1 1.18 mmol/L, whereas the standard group's level was 5.07 0.208 mmol/L. The blood glucose level of the control group was 4.3 0.321 mmol/L. The levels of cortisol in the serum were 1.06 0.23 and 0.92 0.02 ug/dl for herbal and conventional group medications, respectively, but the level in the control group was 1.67 0.499 ug/dl. A morphological study of the spleen was carried out in order to evaluate and compare the efficacy of herbal and standard drugs against stress.Rats in the control group had a spleen weight of 0.250.011 gm, whereas those in the standard group weighed 0.300.009 gm, and those in the herbal combination group weighed 0.320.015 gm, as shown in the table above. The control group's spleen size shrank as a result of stress induction, whereas that of the experimental and comparison groups was much larger. In conclusion, it seems that herbal plants have the potential to lower stress within normal ranges, although further research is required to substantiate these claims.

Chapter -08

Reference

8.Reference

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