Sharma P et al., (2010) investigated two new compounds viz. 4-oxooctyl-2-hydroxyundecanoate and heptacosane-3-enyl-5-hydroxy-hexanoate from the stem of the Nerium oleander.

Barbosa RR et al., (2008) reported following signs of toxicity such as apathy, colic, vocalizations, hyperpnoea (increased respiratory rate), polyuria and moderate rumen distention after oral administration of leaves of Nerium oleander at dose of 50 mg/kg (continuous 6 days), 110 mg/kg (on 7th day continuous 4 dose at one-hourly interval), and 330 mg/kg (last dose on 7th day) in goats. Microscopic evaluation revealed renal necrosis at convoluted and collector tubules and slight myocardial degradation.

Al-Farwachi MI et al., (2008) worked on various clinical parameters, such as postmortem, hematological and biochemical changes in rabbits with median lethal dose of aqueous extract of fresh leaves of Nerium oleander (157.37 mg/kg body weight) when injected subcutaneously. They observed various toxic sign on the second day after administration of median lethal dose crying, ataxia, abdominal respiration, increases in body temperature and loss in the body weight. Also, found hematological as well as biochemical changes include increase in the packed cell volume and hemoglobin concentration and erythrocyte count and leukocytosis with neutrophilia and lymphopenia. Significant increase is also been observed in the aspartate and alanine aminotransferase activities, serum sodium and potassium ions, and inhibition in blood cholinesterase activity in both erythrocytes and plasma within 2-24 hrs after injection.

Yassin MM et al., (2007) studied the protective effect of glimepiride and Nerium oleander on the lipid profile, body growth rate and renal function in streptozotocin-induced diabetic rats. The animals are divided in two groups: control and experimental, the experimental group received the dose of 50 mg/kg body weight of streptozotocin intraperitoneally. Rats with the glucose levels > 200 mg/dl were divided into three subgroups: first group is untreated while those in second and third group were orally administered with 0.1 mg/kg body weight daily glimepiride and 250 mg/kg body weight daily with Nerium oleander extract respectively for 4 weeks. The result showed that in the streptozotocin induced diabetic rats the serum triglyceride cholesterol was significantly increased whereas the body growth was markedly decreased. The uric acid, creatinine, urea concentrations was elevated. Treatment of diabetic rats with glimepiride
or *Nerium oleander* extract improved all the parameters thus indicating their antidiabetic effect.

**AL-Farwachi MI et al., (2007)** determined that *Nerium oleander* has marked immunomodulatory effect on the rabbit immune system. Treatment with dose of 75 mg/kg body weight of leaves extract in rabbits diminish the production of antibodies and also exerted and inhibition on delay hypersensitivity reaction and phagocytic activity, whereas treatment with lower dose 50 and 25 mg/kg body weight subcutaneously caused stimulation of immune system.

**Emanuele E et al., (2006)** reported that the oleandrin could protect the gentamicin induced ototoxicity via the inhibition of the activator protein-1 and C-Jun-terminal Kinase. This effect could be achieved via tropical administration of the polyphenolic glycoside Oleandrin (Anvirzel\textsuperscript{TM}). Anvirzel\textsuperscript{TM} is the aqueous extract of the *Nerium oleander* which is also under investigation as a novel antiproliferative compound. These findings provide a molecular rationale of using Oleanderin to protect against sensorinerual hearing loss after administration of gentamicin.

**Newman RA et al., (2005)** demonstrated that the incubation of human malignant melanoma BRO cells with oleanderin results in time dependent formation of the reactive oxygen species (ROS). This formation of superoxide anion is correlated with a loss in cellular viability, proliferation and cellular defense mechanism such as GSH content. Use of the Mito-SOX and dihydroethidine dyes revealed the presence of oleandrin mediated superoxide anions. Oleandrin also resulted in unusual time-dependent mitochondrial condensation in BRO cells. Thus the exposure of human tumor cells such as BRO to oleandrin results in the formation of superoxide anion radical that mediate mitochondrial injury and loss of cellular GSH pools. This mechanism plays an important role in cardiac glycoside mediated tumor cell injury.

**Liwei Fu et al., (2005)** isolated new urasne type triterpene 1, oleanane –type triterpene 2 and dammarane-type triterpene 15 are the three new triterpene from the leaves of the *Nerium oleander* together with 12 known triterpenes, 3β,27-dihydroxy-12-ursen-28-oic acid (ursolic acid), 3β,27-dihydroxy-12-ursen-28-oic acid, 3β,13β-dihydroxyurs-11-en-28-oic acid, 3β-hydroxyurs-12-en-28-aldehyde, 28-norurs-12-en-3β-ol, urs-12-en-3β,28-diol, urs-12-en-3β-ol, 3β-hydroxy-12-oleanen-28-oic acid (Oleanolic acid), 3β,27-dihydroxy-12-oleane-28-oicacid, 3β-hydroxy-20(29)-lipen-28-oic acid (Betulinic acid),
Chapter – II

20(29)lupene-3β,28-diol(Betulin) and (20S,24R)-epoxydammarane-3β,25-diol. The seven isolated compound and the methyl esters of Urosolic acid and Oleanoic acid reported to produce anti-inflammatory as it inhibit intracellular adhesion molecule-1 (ICAM-1). These compounds also reported to have anticancer activity.

Afaq F et al., (2004) oleandrin application to mouse skin resulted in inhibition of TPA-induced activation of Nuclear Factor-Kappa B (NFκβ) and Ikβα. So it could be useful antitumor promoting agent, because it inhibits several biomarkers of TPA induced tumor promotion.

Hussain MA and Gorsi MS, (2004) studied antimicrobial activity of N. oleander roots, bark and leaf extracts against Bacillus pumilus, B. subtilis, Staphylococcus aureus, E. coli, and Aspergillus niger. The chloroform, ethanol and ethanol-methanol extracts of N. oleander showed high activity against Aspergillus niger. These results were compared with that of the zones of inhibition produced by commercially available standard antibiotics. The inhibitory effects of extracts have been comparable with the standard antibiotics used.

Aslani MR et al., (2004) observed when dried leaves of Nerium oleander was administered orally at single lethal dose (110 mg/kg body weight) in six male sheep produces toxicity in about 30 min along with decrease in heart rate followed by cardiac pauses and tachyarrhythmia, ruminal atony, mild to moderate tympany, abdominal pain, polyuria and polakiuria. Electrocardiography revealed bradycardia, artio-ventricular blocks, depression of S-T segments, ventricular premature beats and tachycardia and ventricular fibrillation. In necropsy there was varying degree of haemorrhages in different organs and gastroenteritis and histopathological examination revealed myocardial degradation and necrosis, degradation and focal necrosis of hepatocytes, necrosis of tubular epithelium in kidneys, edema in lungs and ischemic changes in the cerebrum.

Chowdhury MGA et al., (2004) observed toxic effect with single oral dose of Nerium oleander in 36 adult male guinea pigs divided into six equal groups. Crude watery extract of oleander at dose of 300-900 mg/kg body weight produces nausea, anorexia, dullness, depression, restlessness, abdominal pain, salivation, tremor, respiratory distress, paralysis of limbs and convulsion followed by death. 300 mg/kg body weight dose is
non-lethal and other higher dose 450, 600, 750 and 900 mg/kg body weight caused 17%, 50%, 83% and 100% mortality respectively having LD<sub>50</sub> 540 mg/kg body weight.

**Erdemoglu N et al., (2003)** reported that dried and fresh flowers of *N. oleander* exhibited potent anti-inflammatory activity against carrageenan induced hind-paw edema model in mice without inducing any gastric damage. *N. oleander* has been found to posses potent anti-nociceptive and anti-inflammatory activity.

**Sreenivasam Y et al., (2003)** reported that Oleandrin, active constituent of *Nerium oleander* has its effect on NF-κB and Activator Protein-1 (AP-1) activation and also in apoptosis induced by Ceramide (N-acetyl-D-sphingosine). Ceramide is a second messenger for cell signaling induces transcription factors like NF-κB and AP-1 and also involved in the inflammation and apoptosis. So the compound that inhibits the activation of NF-κB and AP-1 can also block tumorigenesis and inflammation. This suppression of NF-κB coincided with AP-1 causes lipid peroxidation, cytotoxicity, caspase activation and DNA fragmentation. So it was concluded that *Nerium oleander* has anticarcinogenic, anti-inflammatory and modulatory effects.

**Adome RO et al., (2003)** reported effect of crude ethanolic extract of *Nerium oleander* dried leaves having similar action to digoxin on isolated guinea pig heart. Measured following parameters: Force of contraction, heart rate and cardiac flow. The extract produces the dose-dependent increase in all these parameters. This finding provides strong evidence that this herb can be used in the cardiovascular illness.

**Haeba MH et al., (2002)** found out non-lethal dose 1000 mg/kg body weight of 70% hydroalcoholic extract of *Nerium oleander* dry leaves injected subcutaneously into male and female mice once in a week for 9 weeks (total 10 doses) produces gain in body weight and depression. Multiple exposure in the mice failed to produce various changes in the blood parameters (such as WBC, RBC, Hb, HCT, PLT) as well as in the myocardial while lethal dose (4000 mg/kg body weight) induces progressive change in the myocardial electric activity ending up in the cardiac arrest. These electrocardiogram abnormalities are observed due to inhibition of Na⁺, K⁺ ATPase pump.

**Adam SEI et al., (2001)** found that the oral administration of *Citrullus colocynthis* fruits (0.25 g/kg/day) and *Nerium oleander* leaves (0.25 g/kg) or mixture (0.25 g/kg) of both, in 12 sheep. The daily use of 0.25 g of *Citrullus colocynthis* per kg for 42 days was not
fatal to sheep and caused various toxic symptoms like slight diarrhoea, catarrhal enteritis, centrilobular hepatocellular fatty change and degeneration of the renal tubular cells. Single oral dose of *Nerium oleander* (0.25 g) may produces fatal sign and symptoms within 18-24 hr uneasiness, teeth clenching, dyspnoea, anorexia, frequent urination, ataxia and even death are most prominent ones. Various changes in the level of serum lactic dehydrogenase (LDH) and aspartate transaminase (AST) have been observed. Concentration of cholesterol, albumin, globulin, urea and hematological parameters also get changed.

**Smith AJ et al., (2001)** reported Anvirzel is the *Nerium oleander* plant extract contain oleandrin and oleandrigenin two important constituents having potent antitumor activity. These two important constituents inhibit fibroblast growth factor (FGE-2) from two human prostate cancer cell lines DU145 and PC3. Oleandrin (0.1ng/ml) produces a 45.7% inhibition of FGE-2 release from PC3 cells and 49.9% inhibition from DU145 cells.

**Shazly-EL MM et al., (2000)** observed that the ethanolic extract of the *Nerium oleander* leaves contain a potent cardiotonic glycoside neriifolin that has insecticidal activity. This ethanolic extract was also tested for its mutagenicity and mammalian cytotoxicity. Cytotoxicity test revealed that the LC$_{50}$ was approximately 200 rpm while mutagenicity was very low as compared to the standard active mutagen.

**Manna SK et al., (2000)** observed that Oleandrin, a polyphenolic cardiac glycoside derived from the leaves of *N. oleander* could suppress the activation of nuclear factor kβ (NFκβ) and was found to block AP-1 activation induced by TNF and other agents. It inhibited the TNF-induced activation of c-Jun amino terminal kinase. This provides a molecular basis for the ability of Oleandrin to suppress inflammation and perhaps tumor genesis.

**Al-Yahya MA et al., (2000)** investigated that diet containing 10% of *Citrullus colocynthis* or 10% of *Nerium oleander* leaves or their 1:1 mixture (5% + 5%) in rats for 6 weeks produces toxicity symptoms dullness, ruffled hair, decreased body weight gain and feed efficiency. Organ lesions accompanied by leucopenia, anemia and alterations in serum AST, ALT, ALP activites and total protein concentration, albumin, urea, bilirubin and other serum constituents were also observed. Feeding mixture of *Citrullus*
colocynthis and *Nerium oleander* can also produce more marked effects and even death in rats.

**Huq MM et al., (1999)** reported two new cardenolides from the roots of the *Nerium oleander* namely 3β-hydroxy-5α-carda-14(15), 20(22)-dienolide and 3β-O-(D-digitalosyl)-22-hydroxy-5β-carda-8,14,16,20(22)-tetraenolide and two known compound Proceragenin and Neridienone A that are isolated from the roots of *Nerium oleander*. These compounds possess moderate antibacterial activity against *Bacillus subtilis*, *B.cereus*, *E.coli* and *Pseudomonas aeruginosa*. It also possesses strong cardio-stimulating effect on the intact toad heart.

**Begum S et al., (1999)** isolated various cardenolide having CNS depressant activity including new cardenolide, neridiginoside and three known constituents, nerizoside, neritaloside and odoroside-H. At dose of 25 mg/kg methanolic extract of *Nerium oleander* fresh uncrushed leaves exhibit CNS depressant activity in mice due to presence of these compounds.

**Huq Jabbar MM et al., (1998)** Isolated new cardenolides from *Nerium oleander* roots and their structure elucidated as 33β-hydroxy-5α-carda-8, 14, 16, 20 (22)–tetraenolide.

**Siddiqui BS et al., (1997)** isolated two new cardenolides from the leaves of *N. oleander* following a bioactivity directed isolation of the methanol extract, which showed CNS depressant activity in mice at a dosage of 50 mg/kg, i.p.


**Sabira B et al., (1997)** isolated two triterpenoids from the leaves of the *Nerium oleander* namely neriumin and neriuminin which are characterized as 3β, 27-dihdroxy-urs-18-en-13, 28-olide and 3β, 22α, 28-trihydroxy-25-nor-lup-1(10), 20(29)-dien-2-one respectively.

**Elizabeth RT et al., (1996)** determined oleander glycosides in gastrointestinal contents (stomach, rumen, colon and cecum contents) by High Performance Liquid Chromatography (HPLC) Fluorescence method. This method provided an evidence of
the presence of Oleandrin, which is one of the most active cardiac glycoside which produces higher level of toxicity in the *Nerium oleander*.

**Shannon DL et al., (1996)** investigated that *Nerium oleander* contain cardenolide that are capable of exerting positive inotropic effect on the heart of animal as well as on humans. The physiological action of oleander cardenolide is similar to that of digitalis glycoside i.e. inhibition of plasmalemma Na\(^+\) K\(^+\)ATPase.

**Siddiqui BS et al., (1995)** investigated the two cytotoxic pentacyclic triterpenoids from the leaves of *Nerium oleander* namely 3, 3 Hydroxy-28-Z-p-coumaroyloxy-urs-12-en-27-oic acids (cis-karenin) and 3β-hydroxy-28-E-p-coumaroyloxy-urs-12-en-27-oic acid (trans-karenin) with ED\(_{50}\) 15.0 and 7.5 µg/ml respectively.

**Fumiko A et al., (1995)** reported cardenolide glycosides from larvae of the Daphnis nerii reared on the oleander leaves.


**Mazaumder PK et al., (1994)** reported that the methanolic leaf extract of the *Nerium oleander* in a dose dependent manner potentiated both spontaneous and electrical evoked contractions of vas deferens in rats and also in guinea pigs. The methanolic leaf extract also inhibits electrically stimulated neurogenic twitch responses and also evoked a persistent depolarizing effect in the rat phrenic nerve diaphragm preparation. The most prominent effect of this extract was seen on the isolated right atrial preparation in rats, as it inhibit the rate of spontaneously beating atria in the concentration dependent manner.

**Suleiman KD et al., (1993)** obtained various fractions from the aqueous extract of leaves of *Nerium oleander* have been tested against strains of *Proteus vulgaris, Pseudomonus aeruginosa, Shigella flexneri, Salmonella typhimurium, E. coli, Bacillus subtilis* and *Staphylococcus aureus*. Neutral and acidic fractions have been found most active against *P. aeruginosaz*.

**Abe F and Yamauchi T. (1992)** obtained polar glycosides from the air-dried leaves have been re-examined, and gentiobiosyl- nerigoside and gentiobiosyl-beaumontoside
have been isolated along with the major trioside, gentiobiosyl-oleandrin. Minor triosides also include glycosides of 8β-hydroxy-and δ16-8β-hydroxy-digitoxigenin, and δ16-neriagenin, along with glycosides of known cardenolides.

**Siddiqui S et al., (1989)** isolated two pentacyclic triterpenes, kanerin and 12, 13-dihydroursolic acid from the uncrushed, winter leaves of *N. oleander* and there have been established as 24-nor-3β,5-dihydroxyursa-4(23),18-dien-28-oic acid and 3β-hydroxyursa-28-oic acid.

**Siddiqui S et al., (1988)** isolated a new pentacyclic triterpene, oleanderol, betulin, betulinic acid, ursolic acid and oleanolic acid from the fresh leaves of *N. oleander*. These triterpenes have shown CNS depressant activity in mice.

**Siddiqui S et al., (1988)** isolated labdane diterpene, oleanderoic, triterpene and oleanderen from the fresh, undried and uncrushed leaves of *N. oleander*. Their structures have been established as 8α-methoxylabdan-18-oic acid, and 12-ursene.


**Muller BM et al., (1991)** investigated that the water extraction of the crushed leaves of the Nerium oleander yield 2.3% of the polysaccharide while the main fraction contain peptic polysaccharide composed of galacturonic acids. These polysaccharides may contribute to the phagocytosis activity.

**Salimuzzaman S et al., (1990)** presented that “Oleandrin” was the cardiotonic principle in the *Nerium oleander*. Apart from the Oleandrin a series of cardiac and other steroidal and no steroidal glycosides were also present. One of the glycosides folinerin is treated same as glycoside as Oleandrin. Foliandrin is a pure glycoside isolated from *Palestinian oleander* bush and resembles with stropanthin glycoside. Neriodin, glycoside obtained from the dried leaves, it was twice as active as digitoxin like action and has similarity in action with Oleandrin. Number of other cardenolide are obtained from the oven dried leaves oleandrin, adynerin, odoroside A and oleandrigenin. Bark, Trunk and Root of *Nerium oleander* may contain mono, di and triglyceride of pregnenolone and other steroids. A cardio kinetic and diuretic glconerigoside is also isolated from the leaves.
Digitoxigenin-α-L-oleandroside is a rare glycoside obtained from *Nerium oleander*. Later on it was found that *Oleander* also contains cardenolide, oleaside A-F. In recent studies it was founded that there is quantative variation in cardiac glycosides obtained from the leaves of the plant. Thus it is concluded that plant study should fall in two groups based on the content of adynerin and oleaside-A or gentiobiosides adynerin and oleaside-E. Besides the cardiac and other steroidal glycosides *Nerium oleander* also contain some glycosides containing coumarins or flavanoidal aglycones as well as free steroidal constituents such as Neriaside, Neridienone-A, NeriumosideA-1, Odoroside-E, and Odoroside-G.

Salimuzzaman *et al.*, (1989) isolated two new pentacyclic triterpenes namely Kanerin and 12, 13-dihydoursolic acid are from the fresh, uncrushed, winter leaves of *Nerium oleander*. Their structures have been established as 24-nor-3β, 5-dihydroxyusa-4(23), 18-dien-28-oic acid and 3β-hydroxyusa-28-oic acid respectively.

Siddiqui *et al.*, (1986) isolated two new triterpenoids from the fresh, undried, uncrushed leaves of the Nerium oleander namely neriucomaric and isoneriucomaric acid.

Zia *et al.*, (1995) observed B-1 and B-3 fraction of methanolic extract of fresh dried leaves of the *Nerium oleander* produce significant reduction in locomotor activity, rotaroad performance and potentiation of hexobarbital sleeping time. These fractions also reported to have analgesic activity. When these fractions were tested against picrotoxin then fraction B-1 produced 40% protection against convulsions while the fraction B-3 exhibit 60% protection against the convulsions concluding that it has CNS depressant action.

Haque *et al.*, (1993) reported that neutral fraction (N-1) obtained from the leaves of the *Nerium oleander* produce sedation at the low doses, while at higher doses it produces hypnosis. In addition to that it produces marked suppression of locomotor activity. It also blocked the convulsions induced by the GABA receptor antagonist, picrotoxin and bicuculline and enhanced oxotremorine-induced tremor.

Bor *et al.*, (1988) observed that the extract obtained from the *Nerium oleander* at certain concentration appear to stimulate phagocytosis. Thus the extract promotes the healing process and significantly prolonged the life of patients with metastatic cancer disease.
Alzheimer Disease

Bonda DJ et al., (2010) studied the mechanism to prevent the oxidative damage in the AD. They have given the insight into the development of potential treatment regimens and the possibility of a preventative cure. They elaborated the dynamic role of oxidative stress in AD and present corresponding treatment strategies that are currently under investigation.

Hussein MSH et al., (2010) studied the protective effect of vitamin-E against the neurotoxic effect of aluminum chloride in male albino rat. The study confirms that vitamin-E supplementation resulted in a marked appreciable improvement in abnormal alteration observed in AlCl$_3$ treated rats. Therefore, the study revealed that Vit E has a potential ability to exhibit neuroprotective role in conditions of Al-induced oxidative stress and neurotoxic effect in rat brain.

Ray B et al., (2009) unmasked the basics of research on molecular mechanism in different neurodegenerative disorders, including AD, to find new drug targets. He also enlisted the present FDA approved treatments available for AD including cholinesterase inhibitors, role of statins in AD, Role of NMDA receptor and antagonists, Role of PPAR agonists, Use of gamma secretase inhibitor to block the Aβ-mediated amyloidogenic pathways and role of NSAIDs.

Lu J et al., (2009) found that trace amount of copper in mice fed on high fat cholesterol diet leads to Aβ accumulation along with the production of oxidative free radicals leading to the neuronal injury ultimately causing symptoms of AD.

Crouch PJ et al., (2008) revealed the mechanism related to Aβ neurodegenration and discussed the numerous dysfunctional mechanisms that have been associated with AD, ranging from protein aggregation and oxidative stress to biometal dyshomeostasis and mitochondrial failure.

Hussain SA et al., (2008) studied the anti-inflammatory potential of silymarin in patients with knee osteoarthritis and found that Silymarin reduces significantly serum levels of IL1-α and IL-8, C3 and C4 after 8 weeks compared to the pre-treatment levels.

Findeis MA, (2007) explained the central role of amyloid precursor protein (APP) processing and amyloid β peptide (Aβ) production in the risk, onset, and progression of
the neurodegenerative disorder Alzheimer's disease (AD), the most common form of dementia which affects the population of older age. He also suggested the possible therapeutic approaches based on the amyloid $\beta$ excess.

Heneka MT, (2006) revealed the details of the cellular components of neuroinflammation in AD. He also provided the details of pro-inflammatory mediators of inflammation in AD. He mentioned that inflammation significantly contributes to the pathogenesis of AD. The generation and secretion of pro-inflammatory mediators may interact at multiple levels with neurodegeneration. Thus, pro-inflammatory cytokines may not only contribute to neuronal death, but are influencing classical neurodegenerative pathways such as APP and tau phosphorylation. The concomitant release of anti-inflammatory mediators may partly antagonize this action ultimately leading to the chronicity of the disease.

Burgess BL et al., (2006) found that elevated plasma triglyceride levels precede amyloid deposition in AD mouse models with abundant A$\beta$. Cholesterol has a complex relationship with the pathogenesis of AD. It is clear that intracellular cholesterol levels play critical roles in the processing of APP by secretases. This study was specifically designed to challenge the assumption that baseline plasma lipid levels are unchanged in transgenic animal models of AD compared to nontransgenic littermates during the natural history of disease.

Pradhan SC et al., (2006) presented a review on the various reported biological activities of the silymarin and related flavonoids from the plant *Silymarin marianum*. They conclude that silymarin acts by antioxidative, anti-lipid peroxidative, antifibrotic, anti-inflammatory, membrane stabilizing, immunomodulatory and liver regenerating mechanisms. Silymarin has clinical applications in alcoholic liver diseases, liver cirrhosis, amanita mushroom poisoning, viral hepatitis, toxic and drug induced liver diseases.

Balian S et al., (2006) evaluated the anti-inflammatory potential of silymarin in rats. They found that the leaf and leaf callus of Silybum marianum inhibited the formation of paw oedema to significant levels in rats treated either with carrageenan or formalin.
Becaria A et al., (2006) reported that in animal models of AD, exposure to aluminum (Al) or copper (Cu) enhanced oxidative events and accumulation of Aβ peptides. They evaluated the role of aluminium and copper in the neuronal damage and oxidative stress production which ultimately leads to neuronal death resulting in neurodegenerative disorder.

Winocur G et al., (2005) studied the effect of the high fat diet on the learning and memory process in the rat model. They premeditated that rats fed with diets high in saturated or unsaturated fat for 3 months, were severely impaired on a range of learning and memory tasks. They showed that these effects were modulated by concentration of fat, environmental influences, and treatment with glucose.

Reiss AB et al., (2004) discussed the mechanisms for the regulation of intracellular cholesterol levels in various parts of brain and vascular cells that are of considerable importance in our understanding of the pathogenesis of a variety of diseases, particularly atherosclerosis and AD.

Verdile G et al., (2004) explained the Aβ peptide tendency to aggregate, its neurotoxicity and genetic linkage studies, which have led to a hypothesis of AD pathogenesis. According to them an increased production of Aβ results in neurodegeneration and ultimately dementia through a cascade of events.

Morgan C et al., (2004) focused on the structure and function of amyloid deposits. According to them amyloid formation is a process in which normal well-folded cellular proteins undergo a self-assembly process that leads to the formation of large and ordered protein structures. They discussed the process of Amyloid deposition, the structure adopted by these assemblies as well as their functional relationship with cell biology and their potential role in the AD.

McGeer EG et al., (2003) concluded the different components of inflammation in the pathology of AD. They mentioned the various inflammatory mediators like interleukin, tumor necrosis factor etc that are involved in the AD and also suggested the possible use of antiinflammatory agents in the therapeutics of AD.

level of brain was assessed, histological sections of brain were examined and amino acid transmitters contents were detected by reversed phase high performance liquid chromatography. The results of the study revealed that aluminum levels were high in brain specimens of the treated groups comparing to the control and it was dose-dependent. Marked increase in glutamate levels was noticed while GABA level was significantly decreased.

**Behl C et al., (2002)** discussed the role of oxidative damage in AD, antioxidant neuroprotection and possible therapeutic approaches to combat oxidative stress in AD. He added that Antioxidants that prevent the detrimental consequences of ROS can be consequently considered to be a promising approach to neuroprotection and preventing the occurrence of AD.

**Kontush A, (2001)** revealed that increased production of amyloid β as a culprit of oxidative stress in aging and postulated to represent a major event in the development of AD. The key pathological feature behind the AD is suggested to be increased production of Aβ in a form of lipoprotein antioxidant under the action of increased oxidative stress in aging with subsequent chelation of transition metal ions and accumulation of Aβ-metal lipoprotein complexes along with production of ROS.

**Butterfield DA et al., (2001)** stated the evidences of oxidative damage by Aβ and discussed various oxidative biomarkers and their role in AD. They discussed the consequences of oxidative stress associated with lipid peroxidation, protein oxidation, DNA and RNA oxidation in AD.

**McGeer ED et al., (1998)** discussed the role of prostaglandins (PG), amyloid plaques, complement system and inflammatory cytokines in the AD. He suggested that a multitude of mechanisms and general principles that can be exploited in the future to treat the AD. According to author if agents with completely different actions are simultaneously employed, they should have additive, or even synergistic effects and control in AD and other inflammatory disorders may be enhanced.

**Multhaup G, (1997)** summarized the role of Aβ, copper in AD. He considered the interaction of copper molecule with amyloid plaques which leads to the oxidative stress and ultimately results in neuronal damage resulting in AD.
Edelberg HK, (1996) discussed the mechanism involved in the aging and development of brain. He explained the pathological hallmarks of AD as amyloid angiopathy (AA), neuritic plaques (NP), and NFTs. The study suggested the key elements of a proposed multi-step pathogenic pathway in AD focusing on the production of NP.

Mullen R et al., (1996) described the various associated symptoms of AD like depression and other neurobehavioral problems. He also discussed the co-occurrence of depressed mood with preserved insight in AD.

Hodges H, (1996) compared the two spatial memory testing systems morris water maze and radial arm maze. The author indicated their utilization in the behavioural pharmacology with special emphasis on the spatial memory.
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