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A Review on N-Acetylcysteine: Mechanism of Action, Uses, Side Effects.

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Abstract: -

As a dietary supplement, N-acetyl cysteine (NAC) is a widely used antioxidant both in vitro and in vivo. L-cysteine's precursor, NAC, causes the manufacture of glutathione to increase. It scavenges free radicals, particularly oxygen radicals, directly. NAC has strong antioxidant properties. As an adjuvant, N-acetylcysteine may help treat several illnesses, particularly chronic ones. It can also be helpful as a chelator for heavy metals and nanoparticles. These conditions include polycystic ovary disease, male infertility, sleep apnea, acquired immune deficiency syndrome, influenza, parkinsonism, multiple sclerosis, peripheral neuropathy, stroke outcomes, diabetic neuropathy, Crohn's disease, ulcerative colitis, schizophrenia, bipolar illness, and obsessive-compulsive disorder.

Keywords: -Acetylcysteine, Wound Healing, Acne, Sclerosis.

Introduction: -

For many years, N-acetylcysteine has been widely utilized as a mucolytic agent. As more information on n-acetylcysteine's precise mode of action became available, it was tested for a variety of illnesses. It has shown promise in a few medical specialties, including psychiatry, neurology, nephrology, and pulmonology. Additionally, it has been used as an adjuvant medication to treat HIV, Alzheimer's disease, contrast-induced nephropathy, and chronic obstructive pulmonary disease. [1] A sulfhydryl-containing substance with mucolytic qualities, N-acetylcysteine (NAC) was initially patented in 1960 and its application in medicine was first documentedin1967[2]. [Figure1] shows its nomenclature and chemical structure. Since1969, it has been used clinically to treat cystic fibrosis [3]. Since then, NAC's clinical application has grown to include chronic obstructive pulmonary disease and acetaminophen overdose.

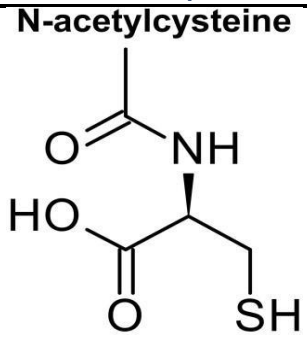

Fig.1 Structure of n-acetyl cysteine

Mechanism Of Action Antioxidant Activity

Oxidative stress, which can harm cellular organelles, is brought on by an excess of reactive oxygen species. The cell contains enzymes such glutathione peroxidase, catalase, superoxide dismutase, and sulfhydryl compounds, of which glutathione is the most crucial, to combat these reactive oxygen species. [4] Glutathione is made up of glutamate, glycine, and cysteine; during stressful situations, the last amino acid restricts its synthesis. [4] N-acetylcysteine replenishes glutathione levels and preserves redox equilibrium in cells by functioning as a cysteine donor. Because it is less poisonous, more soluble in water, and less prone to oxidation N-acetylcysteine is preferable than glutathione or L-cysteine when administered directly. [5]

Modulation In Neurotransmission

Neurotransmitter regulation is another potential way that n-acetylcysteine works. Cysteine dimerizes to create cystine, which raises inhibitory glutamate and is carried across neurons by the cystine-glutamate antiporter. [6] Furthermore, it has been shown that n-acetylcysteine changes the amount of dopamine in neurons. [7]

Anti-Inflammatory Action

In hemodialysis patients, N-acetylcysteine has been demonstratedtolowerIL-6levels.[8] It has also been shown that mice treated with n-acetylcysteine have lower levels of TNF-α and IL-1β.
[9] The redox-sensitive nuclear factor-kappa B, which triggers the expression of pro- inflammatory genes during oxidative stress and causes their lease of a significant quantity of inflammatory cytokines, is inhibited by N-acetylcysteine. [10]

Anti-Proliferative Activity

N-acetylcysteine has been demonstrated to reversibly block the early or mid-G1phaseofthe cell cycle, hence inhibiting NIH3T3 fibroblast cells in mice. Because of this, n-acetylcysteine maybe Used as a medication to stop and reverse fibrosis.[11] It has also been useful intreating hyperproliferative disorders and inhibits the growth of human keratinocytes. [12]

Other Actions

By promoting the synthesis of nitric oxide, N-acetylcysteine also plays a significant part in vasodilation. [13] Additionally, it plays a part in neutrophil activation and microbial attachment.[14]

Followed By MOA

Table No. 1 Mechanism Of Action OF N-acetyl Cysteine

Antioxidant Activity	**Wound Healing, Acne, Psoriasis**
Modulation in Neurotransmission	**Skin Picking Disorder, Subacute Prurigo**
Antiproliferative Activity	**Psoriasis, Systemic Sclerosis**
Anti-Inflammatory Activity	**Contact Dermatitis, TEN**
Vasodilation	**Pseudoporphyria, Wound Healing**
Other Actions	**Nitric Oxide Synthesis**

Uses

In Metabolic Syndrome

Non-alcoholic fatty liver

There is evidence that NAC may help treat metabolic problems associated with nonalcoholic fatty liver disease (NAFLD) by preventing the buildup of hepatic lipids. The main causes of this are the mitigation of lipid peroxidation and antioxidant actions [15]. Most of the preclinical research and a small number of clinical investigations support this, and larger clinical studies are desperately needed. Up to 25% of the population suffers from this illness, which can cause serious pathology such liver fibrosis.

Diabetes

According to research on animals, NAC may enhance lipid profiles and prevent the development of glucose intolerance and hepatic steatosis [16,17]. Short-term (2-week) trials in persons with type 2 diabetes do not seem to show any improvement in ß-cell function or glucose tolerance when NAC is added [18]. Extensive experiments are necessary.

Polycystic Ovarian Syndrome

Women with polycystic ovarian disease may have improved insulin sensitivity after receiving NAC treatment [19]. Although less effective than Metformin in some trials, NAC supplementation demonstrated enhanced fertility in women with polycystic ovarian disease, according to a comprehensive review of RCTs, ovulation, and probabilities of having a live birth [20]. The daily dose in the experiments varied between 1200 and 1800 mg. By lowering neuroinflammation, intravenous NAC May help treat chorioamnionitis, a debilitating illness that increases the likelihood of cerebral palsy and other neurological sequelae [21]. Compared to folic acid alone, it has been demonstrated that using NAC as an adjuvant for recurrent pregnancy loss improves the take- home-baby rate [22].

Hypertension

Cysteine-rich diets such as DASH improve vascular signaling, insulin resistance, oxidative stress, and glycation markers, end products, increase glutathione storage, and lower blood pressure [23].However, blood pressure was unaffected by NAC as an adjuvant treatment in nondiabetic individuals with chronic renal disease who were taking medicine that blocks the renin- angiotensin system[24]. Taking 1800 mg of NAC daily for a month helped middle-aged men with high cholesterol reduce their blood pressure and homocysteine levels. [25]. When NAC and L-arginine are taken together, diabetic individuals' systolic blood pressure improves, and their nitric oxide synthesis rises.

Male Fertility

An RCT employing NAC demonstrated improved oxidative state and semen quality (better motility, viscosity and volume) I idiopathic male infertility [26].600mg was taken twice a day. Semen quality was notably improved in a randomized controlled trial involving combined supplementation with selenium and NAC. [27].

On Various Cancers

Numerous research has examined how NAC affects cancer cells. Both human and cell research seem to gain from altering the environment inside and around the cells.

NAC has been shown to have anti-proliferative effects on breast cancer in a human pilot investigation [28]. NAC significantly lowers the amount of mono-carboxylate transporter 4 (MCT4) transporter proteins that cancer cells need to import lactate as energy. MCT4 is thought to be a sign of aggressive cancer behavior and a low overall survival rate.

NAC was shown to slow the growth of prostate cancer cells and prevent them from spreading or sticking to other areas [29,30]. According to cell research on lung cancer, NAC can scavenge radicals, defend against DNA damage, and detoxify toxins as a precursor of reduced glutathione. Caution is warranted, as a study combining vitamin E and N-acetylcysteine (NAC) demonstrated increased proliferation of mouse and human lung tumor cells, potentially due to a reduction in oxidative stress signaling reactive oxygen species and p53 expression, which promotes tumor growth [31]. Simultaneous administration of N-acetylcysteine (NAC) and epigallocatechin gallate (EGCG), a prominent tea polyphenol, results in the formation of an adduct that may enhance EGCG's cytotoxic effects on cancer cells. [31].

NAC has the amazing capacity to stop tumor growth and cell proliferation in glioblastoma cell experiments [31]. It is necessary to conduct more research on NAC and its application in cancer treatment.

Sleep Apnea

Sleep apnea has grown to be a serious issue that can cause a few cardiovascular conditions, including hypertension and stroke. NAC has been proposed to ameliorate this condition, which is regarded as a pro-inflammatory vascular risk factor [32]. Benefits have been demonstrated in a few modest clinical RCT trials [33, 34,35].

In Infectious Diseases AIDS

TNF-α levels and CD4 counts declined less in the placebo group during a double-blind, placebo-controlled trial, suggesting a more substantial immunomodulatory effect in the treatment arm.800 mg of NAC [36]. NAC raises glutathione levels, which slows down cachexia and wasting and inhibits the effects of inflammatory cytokines [37].

Tuberculosis

In clinical settings, NAC as an adjuvant medication for tuberculosis (TB) treatment led to faster sputum negativity and considerably enhanced radiographic clearance of infiltration and cavity size reduction [38]. TB patients who received NAC during hospitalization had a significantly lower risk of dying within 90 days. [39].

In Neurodegenerative Disorders Parkinson Disease

In neural cell cultures, dopamine may cause apoptosis, which could start the unwarranted loss of nigral cells in Parkinson's disease. NAC and other thiol-based substances protect cell cultures by blocking dopamine-

triggered cell death. [40] Taking 500 mg of NAC twice a day for three months, plus weekly IV infusions, helped improve Parkinson's symptoms and boosted dopamine activity in a clinical study in the brain, which calls for more research [41].

Dementia

Even though beta-amyloid pathology remained unaltered, research on animals has demonstrated great promise in enhancing cognitive performance [42]. Although there is some evidence that NAC, when used as an adjuvant, may reduce the progression of dementia, this effect was shown in a clinical setting in a nutraceutical that contained NAC among other substances [43].

In Eye Conditions Macular Degeneration

In cell investigations, oxidative damage was significantly reduced when NAC was added to retinal pigment epithelial cell cultures [44]. In these cells, NAC also cures lipid peroxidation and Increases decreased glutathione synthesis [45]. Clinical research is necessary because this has been proposed as a revolutionary new treatment for macular degeneration.

Glaucoma

According to current research on animals, NAC may lessen retinal damage brought on by ocular hypertension [46]. Because NAC raises glutathione, it suppresses oxidative stress and autophagy, which may be helpful for some glaucoma patients [47].

Sjogren Syndrome

In one double-blind research, oral NAC was used to reduce halitosis, ocular discomfort, ocular irritation, and daytime thirst in Sjogren's syndrome [48].

In Psychiatric Disorder

Schizophrenia

Glutathione dysregulation in schizophrenia is ameliorated by NAC, a glutathione precursor [49]. A systematic study found that NAC, when administered as an adjuvant therapy, reduces symptoms of schizophrenia and may also improve working memory, one cognitive domain [50]. The lengthier intervention resulted in an improvement.

Obsessive Compulsive Disorder

In an RCT, moderate-to-severe obsessive compulsive disorder (OCD) was significantly improved in the NAC group when NAC was used as an adjuvant with fluoxetine [51]. Resistance/control compulsions significantly improved in children and adolescents treated with citalopram plus NAC as an adjuvant in another RCT [52]. Despite their natively mild side-effect profile, a systematic evaluation of the use of NAC as an adjuvant indicates that results are still unclear [53]. Therefore, larger, more robust studies are necessary to identify which clinical populations would benefit from this. Anxiety symptoms decreased when NAC was given as an adjuvant to treat resistant OCD [54].

Addiction Behavior

In animal experiments, NAC helped reduce relapse in cocaine-seeking behavior by restoring glutamate homeostasis [55]. Early research with NAC in humans has shown decreased urges in substance used disorders [56]. Most of the research on cannabis use disorder, alcohol use disorder, and smoking use disorder showed this, albeit not all of them did.

Table No. 2 Uses

Metabolic Syndrome–Non-Alcoholic Fatty liver, Diabetes, PCOS, Cancer, Male Fertility
Infectious Diseases-AIDS, Tuberculosis
Neurodegenerative Diseases–Parkinson, Dementia
Eye Condition–Macular Degeneration, Glaucoma, Sjogren Syndrome
Psychiatric–Schizophrenia, OCD, Addiction Behavior

Side Effects

When used orally, N-acetylcysteine is generally safe at doses of no more than 2400 mg per day.
[5] Because of its strong, unpleasant taste, the medication must be taken with fruit juice or a soft drink. [57] At this dosage, mild side effects include skin rash, nausea, vomiting, diarrhea, flushing, epigastric discomfort, and constipation. Higher dosages may cause fever, tinnitus, headaches, skin rashes, chills, and urticaria.[58]

When the medication is administered **orally**, adverse effects occur **as least as frequently** as when it is administered **intravenously.** [59] An **anaphylactoid reaction**, which might manifest as urticarial rash, pruritus, angioedema, bronchospasm, and hypotension, can occur when the medication is administered intravenously. This type of reaction, which is thought to be caused by a non-immunological process under the influence of histamine, is more likely to develop in females and in those with atopic diathesis.[60]Although it might not be clinically significant, N- acetylcysteine may potentially disrupt the disulfide bonds in clotting factors and slightly increase the **International Normalized Ratio.** [61] N-acetylcysteine applied topically is usually harmless, though it may cause **moderate adverse effects such burning, erythema, and itching.** [61]

Patients taking nitroglycerin or similar drugs should not take N-acetylcysteine since it can reverse nitrate tolerance and produce **hypotension through vasodilatory effects.** [61] Because there are few studies on pregnant women, n-acetylcysteine should not be used during pregnancy unless absolutely required. Animal studies have revealed questionable embryo toxicity, and there is controversy around the drug's excretion in breast milk and its ability to **pass** through the **placental barrier** during pregnancy. [60]

Table no. 3 Side Effects Of N- acetyl Cysteine

Mild	Moderate	Severe
Skin Rashes Nausea Vomiting Diarrhea	Burning Erythema Itching Chills	Urticaria Tinnitus Hypotension Bronchospasm Angioedema

Result & Discussion

According to an analysis of the NAC literature, this substance is a well-tolerated, safe supplemental medication with few adverse effects. One significant feature of this dietary supplement is its antioxidant and free radical scavenger properties. Patients with polycystic ovarian syndrome who have CC resistance to it, preterm birth, paracetamol toxicity, RPL, persistent bronchitis, colitis with ulcers, liver cancer, muscle

function, hemodialysis, asthma, Alzheimer's disease, and Parkinson's illness have all benefited from its use as a medication. Even said, NAC activity is still unknown in some situations, such as increasing rates of pregnancies in ICSI cycles, and more research is required. NAC treatment appears to have positive effects on ICAM-1 and VCAM 1- levels in vascular dysfunction. To investigate the direction of NAC intake effects on vascular function, a meta-analysis and more clinical studies are required to examine the net effect.

Abbreviations-

NAC–N-acetylcysteine

PCOS–polycystic ovarian syndrome

AIDS–Acquired Immune Deficiency Syndrome

OCD – obsessive compulsive disorder

Figure List

Figure No. 1- Structure of n-acetyl cysteine

Table list

Table no.1- Mechanism Of Action Of N- acetyl cysteine

Table no. 2- Uses

Table no. 3- Side effects of N- acetyl cysteine

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