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Role of Nitric Oxide in Pulpal Tissue Regeneration: A Narrative Review

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ABSTRACT:-

Regeneration in endodontics is an evolving field that uses tissue engineering concepts to regenerate pulp, cementum, enamel, and dentinal structures. Regeneration was initiated by Nygaard-Ostby with the introduction of blood-clot-associated pulpal healing and apical closure. For an ideal regeneration Dental stem cells, scaffolds, growth factors, sterile environment and controlled release of growth factors are essential. Irrigants, medicaments, and antimicrobial agents have been used for canal

disinfection but for stem cells to survive and proliferate, growth factors must be released at the proper concentration in both irrigants and medications. Nitric oxide is regarded as a potential therapeutic agent for its role in wound healing, antimicrobial effect, angiogenesis, and tissue remodeling. Hence, the use of NO as an adjuvant in the regeneration process is being explored. Several modalities, like NO-releasing nanomatrix gel, NO donors, or nitric oxide-releasing compounds (NOCs), are used to deliver nitric oxide within the root canal. This review paper discusses how nitric oxide aids in pulpal tissue regeneration.

INTRODUCTION:-

Regenerative endodontics is defined as "biologically based procedures designed to replace damaged structures, including dentin and root structures, as well as cells of the pulp-dentin complex"[(1)].AAE guidelines recommend that regeneration can be attempted when the pulp is necrotic and the apex is immature, provided that pulp space is not required for the post or core[(2)].It was Nygaard-Ostby, in 1961, who pioneered the use of blood clots for pulp regeneration. This ground breaking work by Nygaard-Ostby opened the door for the tissue engineering of pulp regeneration and showed that these regenerative techniques have become increasingly common over time. It has been demonstrated that there are numerous regenerative techniques currently being used, including pulp implantation, 3D cell printing, postnatal stem cell treatment, scaffold implantation, injectable scaffold administration, and root canal revascularization[(3)]. For successful regeneration, stem cells, morphogens, and the extracellular matrix are critical[(4)]. Furthermore, the development of effective bio compatible scaffolds and biologically-derived materials is required to bridge the gap between tissue engineering and real life applications. Among the numerous types of human dental stem cells that are used for pulpal tissue regeneration, there are five types of stem cells that can be considered as potential stem cells for regeneration. These include tooth germ progenitor cells (TGPCs), dental pulp stem cells (DPSCs), stem cells from exfoliated deciduous teeth (SHED), stem cells from the apical papilla (SCAP), and periodontal ligament stem cells (PDLSCs)[(4)].Acquiring autologous dental stem cells is difficult, and the potential of obtaining a sub population of stem cells is even more arduous, despite the fact that human dental stem cells have potential regenerative therapeutic uses for treating dental diseases such as pulpitis and periodontitis.[(5,6)] For these reasons, researchers have sought to develop efficient methods of isolation and expansion of stem cells from both autologous and allogeneic sources[(7)].The second important factor responsible for regeneration is the controlled release of growth factors. Morphogens are signals released extracellularly that control morphogenesis during interactions between epithelial and mesenchymal cells. Bone morphogenetic

proteins (BMPs), fibroblast growth factors (FGFs), wingless- and int-related proteins (Wnts), hedgehog proteins (Hhs), and tumor necrosis factor (TNF) make up the morphogenetic signaling networks[5,6]. The main problem with growth factors is that different combinations of growth factors are needed to get stem cells from various sources to differentiate in a certain way. The quantity and timing of the growth factor administration present a substantial difficulty, in addition to safety[8]. To provide a three-dimensional physicochemical and biological micro environment, a scaffold can be used. It also encourages cell migration and adhesion as well as growth. The scaffold is a major element of tissue engineering, providing a framework on which cells can attach, proliferate, and differentiate. In protein treatment and cell therapy, the scaffold acts as a carrier for morphogen and cells, respectively, and provides the necessary biochemical and physical cues that influence the behavior of these cells[8]. The ability of the scaffold to transfer waste, oxygen, and nutrients should be effective. It should eventually deteriorate and be replaced by regenerated tissue, keeping the ultimate tissue structure's characteristics. Bio compatibility, non toxicity, and enough physical and mechanical strength are required for the scaffold to be an effective carrier for these treatments. All of these factors must be taken into account when designing an effective scaffold, as they can make the difference between a successful treatment and one that fails[9]. Scaffold-based methods offer the potential to produce a functioning tooth with the desired shape and placement quickly, but they must overcome difficulties with attachment to the jaw, infection, repetitive motion, and load tolerance throughout maturity. In addition, scaffolds must be capable of degrading in a manner that is conducive to the regrowth of tissue[10]. The ideal factors for regeneration are a sterile environment and the controlled release of growth factors. The traditional techniques employed for disinfection of the canals are irrigation of the canals and the placement of intracanal medicaments. However, due to the complexity of the root canal system, it is difficult to ensure complete disinfection. The AAE's current recommended practices of using EDTA, Ca(OH), diluted doses of sodium hypochlorite, and antimicrobial pastes were found to drastically reduce dentin microhardness and result in demineralization[11]. NaOCl deteriorates the viability, proliferation, and differentiation of dental pulp stem cells[12]. Additionally, using antibiotics like minocyline may result in tooth discoloration. Therefore, it is important to consider alternative strategies to achieve ideal regeneration .Hence the usage of nitric oxide in regeneration of pulpal tissue is explored in this review article.

NITRIC OXIDE:-

Nitric oxide is an extremely reactive free radical that is neutral and hydrophobic. It is synthesized by the enzyme nitric oxide synthase (NOS) using L- arginine as the substrate. NO is of two types based on the source: exogenous nitric oxide and endogenous nitric oxide.[13]

NOS enzymes are responsible for the production of endogenous NO. These enzymes, located in various organs, tissues, and cells throughout the body, are involved in a variety of biological processes. All isoforms of NOS produce endogenous NO by consuming L-arginine as a substrate with molecular oxygen (O2), nicotine adenine dinucleotide phosphate (NADPH), and other cofactors (such as adenine dinucleotide (FAD), flavin mononucleotide (FMN), and 6R)5,6,7,8 tetrahydroL-biopterin (BH4)) as cosubstrates. This reaction, known as the NOS-catalyzed reaction, results in the formation of L-citrulline and NO from L-arginine.NO is a relaxing agent generated by the endothelium that can widen blood arteries and lower blood pressure, which was found by Murad, Furchgott, and Ignarro in the 1980s. This ground-breaking finding demonstrated that NO has a crucial function in cardiovascular regulation, modulating vascular tone, heart rate, and blood pressure.[14,15,16]. NO has been discovered to perform a variety of roles in controlling physiological processes, inflammatory processes, and tissue healing events, including cell growth, neuronal degeneration, angiogenesis, and odontoblastic differentiation. NO has well-known functions in physiology, but it is also understood to be involved in a number of pathophysiological conditions, including diabetes, Parkinson's disease, and atherosclerosis[17]. The inflammatory response and cell proliferation processes, which are essential to the healing of wounds, can be controlled by NO. In relatively high quantities, NO can directly destroy microorganisms or actively limit their growth. Additionally, it has been shown that NO can lessen oxidative stress and cell apoptosis, resulting in a faster pace of wound healing[18,17]. NO is a neurotransmitter that mediates respiratory, genitourinary, cardiac, and vasodilator tone by activation of cyclic guanosine monophosphate (c-GMP)[19]. Through perivascular and endothelial cell recruitment, NO considerably aids in promoting angiogenesis and the development of mature blood vessels[19]. The production of vascular endothelial growth factor (VEGF) during angiogenesis, which takes place during bone remodeling, has also been demonstrated to be regulated by NO. This further adds to the evidence that NO has a profound impact on healing, not only by improving the rate at which wounds close but also by contributing to a number of other physiological processes that are necessary for proper wound repair[19]. Moreover, NO acts as an anti-inflammatory agent and serves to promote cell survival while also mediating the production of extracellular matrix molecules and stimulating epithelialization . Furthermore, NO retains the capacity to either directly block bacterial growth or eliminate it and stop infection[15]. NO can also be produced exogenously by nitric oxide donors[20].To be used under various circumstances, donors

were combined with various scaffolds. Polymeric materials are easily manipulated and formed into a wide variety of forms, serving as potent scaffolds for NO loading that can also improve the stability of NO donors and modify the NO release profiles[(20)]. This is especially advantageous as polymers possess a number of features such as bio-compatibility, biodegradability, versatility in chemical and physical modification, and low production costs. Thus, polymeric materials have the potential to be used as drug delivery systems that can precisely deliver NO in a targeted manner and over prolonged periods of time[(13)].

ANTIBIOTIC ROLE OF NO:-

A vital part of the body's defense against infections is played by the short-lived, diatomic, lipophilic gas nitric oxide (NO). Immune cells have the important property of producing NO. Neuronal NOS (nNOS), inducible NOS (iNOS), and endothelial NOS are the three NO synthase (NOS) enzymes that produce most of the NO (eNOS).[(21)]Both eNOS and nNOS function as constitutively expressed proteins, and neither endothelial cells nor neurons are the only tissues in which they are found[(22)].In reality, during infection and autoimmunity, both nNOS and eNOS release NO in various tissues, where they can modulate the release of pro-inflammatory cytokines and chemo-kines. Its multiple roles include participation in immune cell communication and the biochemical processes by which immune cells protect themselves against bacteria, fungi, viruses, and parasites[(23)]. Other activities, including the differentiation, growth, and death of immune cells, are regulated by NO signaling. NO also affects the production of cytokines and chemokines, which regulate the migration and activation of immune cells at infection sites . Furthermore, NO also plays an important role in the development of T helper (Th) cell-mediated adaptive immune responses by promoting Th1 responses and suppressing Th2 responses[(23)]. NO causes nitrosative and oxidative harm to invasive pathogens when it is released by immune cells that have been activated. Due to NO's adaptability, it may swiftly pass through microbial cell membranes and trigger the afore mentioned nitrosative and oxidative processes. The simultaneous evolution of several bacterial mutations is required for microbial resistance to happen. This means that the activation of immune cells releasing NO is an effective defense against many invasive pathogens, as it is difficult for these pathogens to simultaneously evolve several mutations to build resistance[(24)]. NO has the ability to destroy microorganisms at high quantities. Nitrogen dioxide (NO2), peroxynitrite (ONOO), and dinitrogen tetroxide are all highly oxidising chemicals that can be produced when NO, which is unstable in cells, reacts with oxygen or reactive oxygen intermediates such superoxide (O2) and hydrogen peroxide (H2O2) (N2O3).

Reactive substances also attack DNA, resulting to DNA cleavage and deamination through oxidative and deamination damage[6]. There are three ways that NO harms DNA: by directly reacting with the DNA structure, by preventing DNA repair, and by increasing the production of genotoxic alkylating chemicals and hydrogen peroxide. DNA damage is instead brought on by RNOS, which is created when NO undergoes autoxidation[23]. It inhibits DNA repair enzymes associated with the repair of alkylation in DNA[25]. They can also induce lipid peroxidation to damage the cell membranes and cause oxidative damage to proteins, carbohydrates, lipids, and DNA[26] thus resulting in dysfunction and ultimately cell death[18, 27]. The following criteria should be met by no-release materials employed as antibiotics: (1) being simple to construct, (2) being stable during both storage and administration, (3) having adequate NO discharge, (4) having a reasonably lengthy release duration, and (5) being capable of thorough engagement of bacteria[17]. Mainly, two types of NO-derived donors are used in the antibacterial field: N-diazeniumdiolate (NONOate)[28,29]and S-nitrosothiol (RSNO). Hydrophobic NO-releasing xerogel that prolongs the releasing time of NO to ensure a good antibiotic effect is found effective[30]. It has been proven that the antibacterial effect of NO is dose-dependent[31,32]. S-nitrosoN-acetylpenicillamine (SNAP) modified polymers have been shown to release NO consistently for over 2 weeks, but NO concentration was near the lower end of physiological levels[33]. Recently, to overcome the disadvantages, a biomimetic nanomatrix gel that has a combination of antibiotics and NO was proposed to facilitate regeneration. This nanomatrix gel exhibits improved antibacterial properties and more sustained NO release compared to SNAP-modified polymers, suggesting that a combination of antibiotics and NO could be a viable approach for tissue regeneration. This combination of antibiotics and NO has been shown to increase the efficacy of both treatments, as each has its own unique benefits[34].

REGENERATIVE ROLE:-

Numerous cellular processes, including apoptosis, differentiation, neurotransmission, immunological responses, control of vascular tone, platelet aggregation, and angiogenesis, can be regulated by NO[31]. The ATPase activity, a marker of osteoblastic development, was elevated by a NO donor called SNP in a concentration-dependent manner. Additionally, it raised the level of cGMP in the cells, which is the second messenger of NO and the catalyst for osteoblastic differentiation. These results indicated that NO was involved in osteoblastic differentiation and played a critical role in the

development of bone[35]. Diethylamine NONOate, a long-lasting NO donor, elevated the gene expression of osteocalcin, another indicator of osteoblastic development[36]. According to a recent study, runt related factor 2 (Runx2), DMP 1, and dentin sialophosphoprotein, which are genes unique to odontoblasts, might increase alkaline phosphatase (ALP) activity and expression levels in rat dental pulp stem cells (rDPSCs) in the presence of exogenous NO. Additionally, NO induced extracellular signal-regulated kinase (ERK) and protein kinase B (AKT) pathways were activated in rDPSCs, which play an important role in odontoblastic differentiation[37]. In endochondral ossification and bone repair, low doses of NO are associated with rising osteoblast counts, mineral apposition, and bone formation rates via angiogenesis[38,39]. The differentiation of cultured mouse cells is accelerated by exogenous NO production employing S-nitroso-N-acetyl-penicillamine (SNP) as a NO donor[40]. In the latest study, dental pulp tissues showed signs of healing with the production of fibrous, osteoid, and cementoid tissue. This could be indicative of the potential of nitric oxide in controlling inflammation and stimulating the proliferation and differentiation of dental pulp stem cells. These findings were in line with those of other studies, which indicated that newly formed pulp tissues following regenerative endodontic therapy are made up of tissues more similar to those of periodontal, bone, and cementum than those of dentin. Furthermore, these results are also consistent with the hypothesis that NO plays a role in the differentiation of odontoblasts and osteoblasts in order to promote dentinogenesis and cementogenesis[41,42]. These results lend credence to the idea that during the healing process following replantation, the periodontal ligament, bone, and cementum may expand into the pulp canal and that these three tissues may interact and contribute to the formation of the newly formed pulp[43]. According to some studies, this healing reaction may begin and continue even if there is no pulp tissue in the pulp canal[44]. At the beginning of the differentiation process, exogenous NO may firmly commit DPSCs to mature odontoblasts. In addition to pro-inflammatory actions, NO also mediates signals that control cell growth and differentiation[45]. Therefore, it is conceivable that NO functions as one of the regulators of the development of odontoblast-like cells[46]. NO is also implicated in the mineralization of chondrocytes and osteoblasts, suggesting that it may play a role in how odontoblasts produce tertiary dentin as well[47]. Thus, NO-releasing biomaterials could be crucial for the regeneration of pulp-dentine tissue. To deliver NO inside the canal, scaffolds, nanobiomedical devices, triple antibiotic pastes with NO, and biomimetic nanomatrix gel can be used. Exogenous NO delivery mechanisms use the immunoregulatory and antibacterial effects of NO to combat infectious illnesses. There are several different NO delivery systems that have been created, all of which aim to distribute NO in a secure, efficient, and practical way. Technologies are available that vary from simple gaseous NO (gNO) kept in a tank to complicated NO molecules contained in nanoparticles[20]. These

nanoparticles can be synthesized to target a particular region in the body and are made of bio compatible materials such as polymers, lipids, and proteins. Each system has its own unique advantages and limitations, which must be carefully considered when determining which method is best for a particular application. While these are all promising methods for delivering NO to achieve pulp-dentine regeneration, there is a lack of evidence of long-term efficacy due to the challenges associated with monitoring and evaluating clinical outcomes. The biomimetic nanomatrix gel is made of a self-assembled PA matrix produced using a water evaporation process without the use of organic solvents and biocompatible peptide-based material. It shows promise for potential future uses of bio-absorbable stent coatings and may improve structural integrity and eliminate problems with inflammatory reactions[(47)]. The storage and delivery parameters of the NO-releasing nanomatrix gel must be correctly set in order to maximize its stability and effectiveness. Further research is needed to evaluate the safety of employing nitric oxide-releasing polymeric nanomatrices as well as the sustained release of nitric oxide in various simulating physiological situations[(34)]. The regenerative potential of NO-releasing nanomatrix gel is reported to have therapeutic functions in bacterial infections, wound healing, and cardiovascular diseases[(26)].The main disadvantage of NO is its elevated risk of toxicity upon uncontrolled release. To overcome this optimal dosage of NO using local drug delivery systems like scaffolds or gel can be used.

CONCLUSION:-

This literature review discusses the various roles of nitric oxide in the regeneration of pulpal tissue and the importance of optimal dosage of nitric oxide in ensuring that its therapeutic potential is not undermined due to its toxic effects . Various in vivo and in vitro studies have been attempted in regenerative endodontics, as it is a developing field and a minimally invasive endodontic procedure. Nitric oxide has been found to be a promising molecule in the field of regenerative endodontics, as it helps in the regulation of odontoblasts and increases cell proliferation. Nitric oxide has regenerative and antibiotic properties, which are essential for ideal regeneration. Thus, it is evident that nitric oxide plays an important role in regenerative endodontics Further studies are required to understand the conclusive effects of nitric oxide on pupal tissue regeneration.

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