Review Article

Applications of Cold Atmospheric Pressure Plasma In Dentistry- A Review

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ABSTRACT

Plasma is one of the most dominant states of matter in the universe and was identified by Sir William Crooke in 1879. It is an electrically conducting medium that responds to electric and magnetic fields. It implies studies concerning the direct action of low temperature and the effect of low atmospheric plasma pressure on body tissues for various non-invasive therapeutic treatments or diagnostic purposes. Plasma consists of large quantities of highly reactive species, such as ions, energetic electrons, exited atoms and molecules, ultraviolet photons in the meta-stable state, and active radicals. Research has revealed promising and successful medical applications of these non-thermal, cold plasma-reactive oxygen species. The objective of this minor review is to highlight the numerous applications of cold atmospheric pressure plasma (CAPP) in dentistry, which include: dental caries prevention by bacterial inactivation; prevention of oral cancer by selective destruction of the tumour cells and damaged tissue repair effects; tooth bleaching or whitening procedures; in restorative dentistry for placement of composite restorations; in endodontic therapy for root canal disinfection; and for the treatment of oral thrush (induced by *Candida albicans*).

Keywords: Cold Atmospheric Pressure Plasma; Antimicrobial Agent; Plasma Medicine; Dentistry

1. INTRODUCTION

Apart from the three states of matter, namely solid, liquid, and gaseous states, plasma belongs to the metastable state of matter comprised of a gaseous mixture of high energy protons, electrons, reactive oxygen species, and high energy ultraviolet photons at varying densities and different temperatures [1]. Plasmas, unlike conventional matter, it may exist in a wide temperature range without altering state. Plasma was discovered in 1879 by British physicist William Crookes, and Irving Langmuir named it in 1929.
Gas molecules can be heated or exposed to a strong electromagnetic field so as to generate plasma radiation. Plasma is produced by passing high-intensity irradiation such as ultraviolet rays and microwaves through gaseous molecules like oxygen, nitrogen, helium, and argon in the presence of an electrical field [2]. Plasma technology forms the basis for the workings of computers, mobile phones, and various display panels. The successful biomedical applications of plasma irradiation have been proved through research. Cold atmospheric pressure plasma (CAPP) also known as Non thermal plasma (NTP) has enormous biomedical applications as the temperature at the contact site is < 40^0C that minimizes damage to the underlying healthy tissues. Plasma was originally introduced in dentistry to disinfect dental instruments while they were being manufactured. Various researchers investigated the therapeutic applications of plasma in dentistry, which can be divided into

two categories: the use of plasma technology for the treatment of surfaces, materials, or devices, and the direct application of plasma to the human body for therapeutic purposes such as tooth bleaching, root canal disinfection, etc. [3].

2. CLASSIFICATION OF PLASMA

Plasmas are categorised as "thermal" or "non-thermal" based on the relative temperatures of the ions, neutrons, and electrons.

2.1 Thermal Plasma:

This is a natural phenomenon that reflects thermally balanced high-intensity electrons and ions. For many years, medical science has relied on hot plasma procedures like electrosurgery and coagulation to establish hemostasis.

2.2 Non Thermal Plasma (NTP):

Low temperature plasma, often known as "cold plasma," is used to modify the surfaces of biomaterials. It's made by converting a substance to a gas at a low temperature and then applying ionisation energy in the form of heat, direct or alternating electric current, radiation, or laser light. Plasma gas sources include oxygen, nitrogen, hydrogen, and argon [4].

3 GENERATION OF PLASMA:

As they are manufactured in an open environment and can be easily incorporated into online processing, atmospheric pressure plasmas have become a highly desirable technology for material processing applications in recent decades. Permanent necrosis of healthy tissues and damage to heat-sensitive organs are among the harmful effects of hot atmospheric plasma [5]. Inert gases such as oxygen, nitrogen, hydrogen, and argon in their diatomic state when excited by high frequency energy cause dissociation of the gas by the stripping of electrons, thereby resulting in the generation of plasma for irradiation onto the oral tissues [Figure 1].

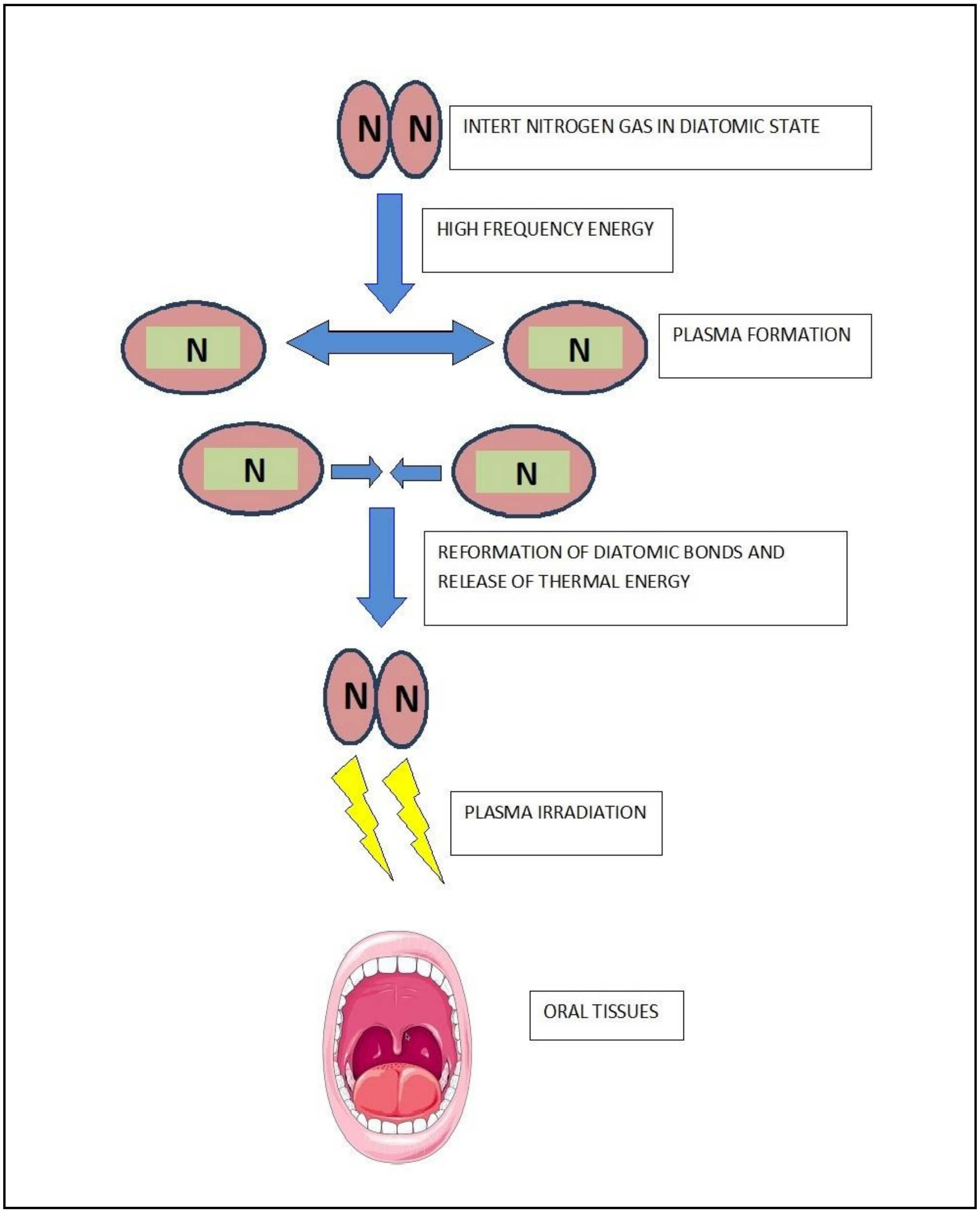

Figure 1 - Nitrogen gas being acted upon by high frequency energy, causing the dissociation of gas by stripping of electrons and generation of plasma [4,5].

4 DEVICES PRODUCING PLASMA:

Plasma can be synthesised using direct current or alternating current, microwaves, and high frequency radio waves. When the electrons in plasma are displaced from their equilibrium positions, strong electrical fields are created between the negatively charged layers and the background positive layers. These electrical fields tend to restore the initial neutral condition by bringing the particles back to their original positions. As a result, the plasma frequency, which is composed of a number of mobile electrons, increases. These electron plasma waves, also known as Langmuir waves, are formed as these oscillations propagate. This high-frequency wave is electrostatic in nature.

4.1 DIELECTRIC BARRIER DISCHARGE

Siemens conducted the first Dielectric Barrier Discharge (DBD) experiments in 1857. Sterilization of living tissue, bacteria inactivation, angiogenesis, surface disinfection, and excimer production are a few of the applications of DBD [6].

The DBD is comprised of two flat metal electrodes that are coated with dielectric material. The two electrodes used include a high-voltage electrode (that generates alternating current with a power consumption of up to 100 W) and a grounded electrode. The flow of a carrier gas between these two electrodes produces plasma [7]. Cooper et al. proposed the concept of the floating electrode DBD (FE-DBD). An insulated high-voltage electrode and an active electrode are used in this method. The second electrode in this device is active (it might be human skin, a sample, or even an organ) and is not grounded. To create the discharge, the distance between the two electrodes must be less than 3 mm. This device is effective on endothelial cells, hence it has various biomedical applications like haemorrhage control and treatment of melanoma [8].

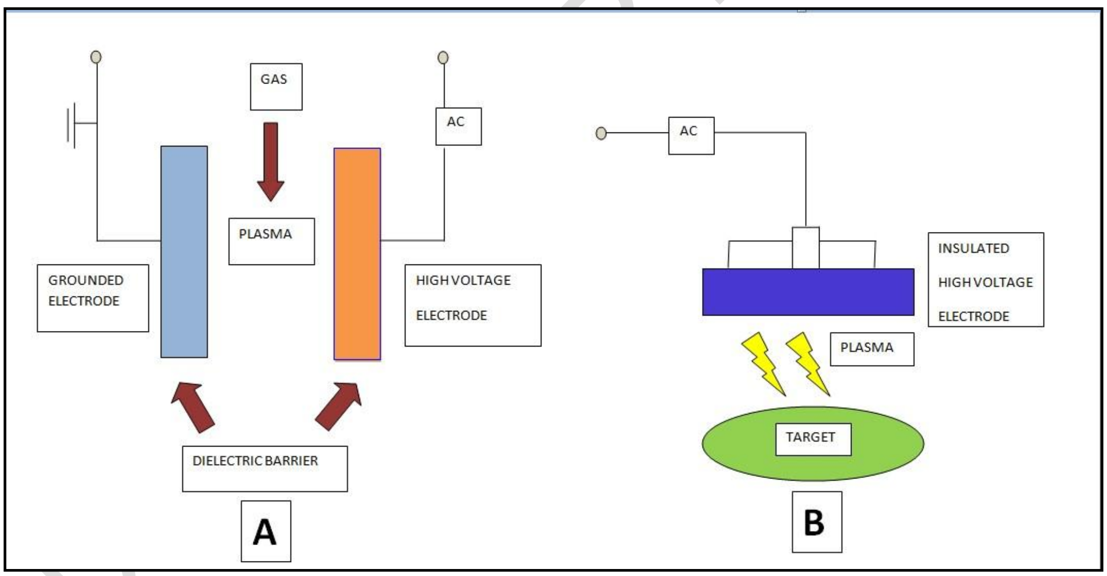

Figure 2: (A) Formation of Plasma by the dielectric barrier (DBD); (B) Floating electrode dielectric barrier discharge (FE-DBD) [6,9].

DBD's gas temperature is near room temperature, making it suitable for biological applications. On the other hand, FE-DBD cannot be used to irradiate plasma inside root canals or internal organs.

Plasma irradiation generated by dielectric enclosure is represented by atmospheric pressure plasma jets (APPJs) (tube or syringe).The expelled plasma is called a plasma plume and is directed towards the target tissue. Figure 2 is a schematic representation of the APPJ

concept. Some recent studies [9] provide further information regarding APPJs and their properties.
The plasma plume tip can be kept below 400 °C depending on the operating circumstances of the jet, allowing contact with biological tissues without risk of burns or electric shock. As a result, CAPP, such as FE-DBD and APPJ, has been recognised as one of the most promising tools for biomedical and hospital applications. [8,9].

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5. MECHANISM OF ACTION

The release of free radicals and reactive species (e.g., reactive oxygen and nitrogen species, i.e., ROS and RNS), Metastables, and UV light form the basis of the mechanism of action of plasma irradiation. The redox signalling system in cells are regulated by these radicals. Electrons accelerate at a much higher rate than heavier ions in the presence of an electromagnetic field. Ionization of particles, radiation, and the formation of reactive species are all caused by accelerated electrons. Argon, hydrogen, oxygen, or nitrogen are the common gas sources for plasma generation. It's effective for wound sterilising and healing since it destroys tumour cells, but it's detrimental for the surrounding healthy cells due to its high concentration. Ozone is produced by non-thermal plasma, according to research. This ozone in aqueous media further generates biologically active ROS and RNS [10].

6. APPLICATIONS OF PLASMA IN DENTISTRY

A new type of plasma technology referred to as "non-thermal atmospheric plasmas", allows surface preparation in the open air at room temperature. Numerous dental applications have been developed. This extensive generation of reactive oxygen species, reactive nitrogen species, meta-stables, and charged particles, is one of the most important characteristics of non-thermal plasma [11].

Physical plasma applications in dentistry can be classified into two major categories:

A) **Surface treatment** of materials or devices are done to improve certain properties for specific applications, such as disinfection. NTAPP was used in chair-side applications for surface treatments. These include the following:
   - Surface modification of Implants
   - Plasma Cleaning and sterilization of Dental Instruments
   - Enhancing adhesive qualities

B) The following are examples of **direct plasma applications** in the human body for therapeutic purposes:
   - Microbicidal activities
   - Treatment of Dental caries
   - Root canal disinfection
   - Tooth Bleaching
   - Oncology
   - Intra Oral Lesions

6.1 SURFACE TREATMENTS OF PLASMA

6.1.1 MODIFICATION OF THE IMPLANT SURFACE TO IMPROVE OSSEOINTEGRATION:

Plasma technology is being employed to alter the implant surface in order to increase osseo-integration. As the implant surface is the first component of the implant to come into contact with the host, efforts are made to accelerate the early host-implant reaction, with an increased focus on rapid bone repair. By altering the surface roughness and wettability, plasma therapy can improve cell adhesion. Plasma therapy lowers the contact angle and supports the spread of osteoblastic cells in chairside operations using NTAPP prior to implant placement [12,13].

6.1.2 FIBRE REINFORCED COMPOSITE POST:

Aesthetic dentistry employs the use of fibre-reinforced composite (FRC) posts for rehabilitation and for core build up of grossly decayed teeth. Plasma irradiation facilitates "monoblock" adhesion between FRC posts and resin composites. However, highly cured FRC posts with firmly cross-linked matrixes prevent efficient adherence to resin cements or composite resin core materials. The surface treatment of fibre posts with plasma improves the hydrophilicity of epoxy polymers due to oxygen-containing functional groups that improve the humectation, that is, the wetting of the post surface along with changing the chemical composition of the surface. Cleaning and ablation of organic contaminants and weak boundary layers; degradation of the polymer chains; formation of radicals on the surfaces; creation of a thin cross-linking layer; and formation of chemical groups on stabilised surfaces are some of the effects of plasma treatment on polymer surfaces. Acid-base interactions and covalent bonds are the results of these effects [14, 15].

6.1.3 WOUND STERILIZATION:

The impact of plasma exposure on microbiological morphology was visually examined using a scanning electron microscope (SEM). According to Hong et al., *E.coli* (Gram negative) cells suffered severe morphological alterations, including lysis, after being exposed to plasma. While in *B.Subtilis* (Gram positive), there are no morphological changes in the cell while there is reduced cell viability, causing cell un-culture [16] The bacteriocidal activity of plasma irradiation is demonstrated by targeting multiple bacterial cell components such as DNA/RNA, lipid, and protein, causing lipid peroxidation and cell lysis [17] [Figure 3].

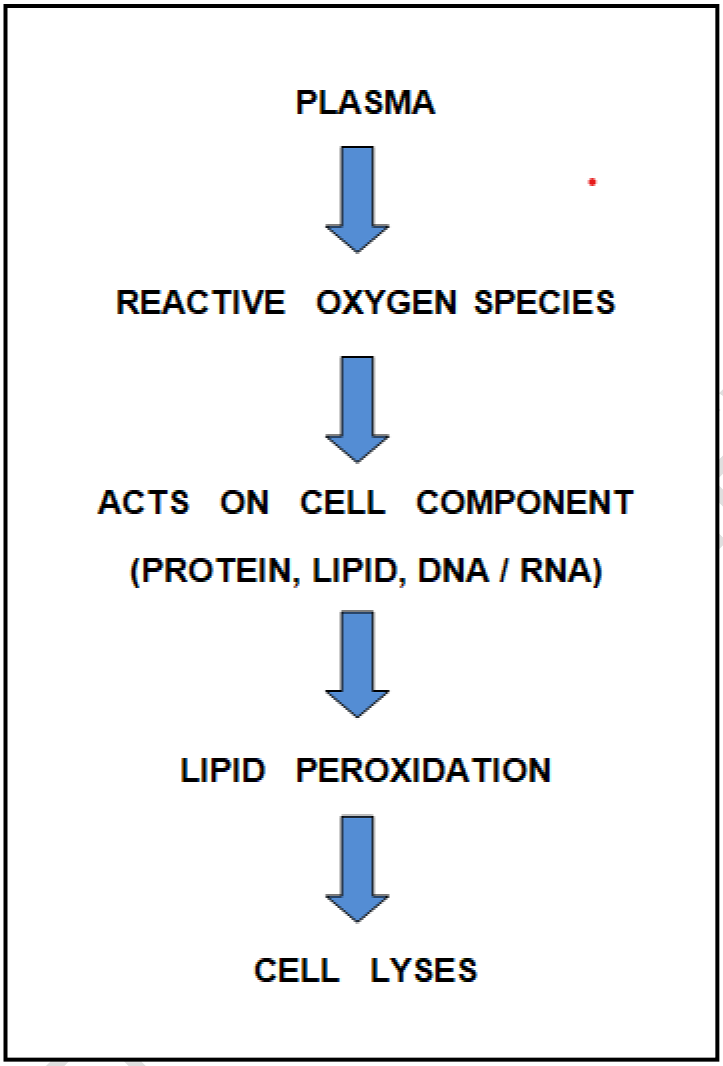

Figure 3 – Schematic representation of the effect of plasma irradiation on bacterial cells [17].

6.1.4 STERLIZATION OF DENTAL INSTRUMENTS:

Due to the direct contact of endodontic files with infected peripheral tissues, sterilization of these instruments is of great concern. Creutzfeldt–Jakob disease (CDJ) is described as a rare group of fatal human diseases with familial, sporadic, and acquired variants. It is identified by an aberrant form of prion protein accumulating in the central nervous system as well as in the pulp. As a result, endodontic files, which come into direct contact with the peripheral tissues, pose an elevated risk of CJD transmission. Hence, using gas plasma irradiation is highly recommended to reduce the risk of transfer of proteinaceous components between the endodontic files and patients when the instruments are reused [18, 19].

6.1.5 PLASMA CLEANING:

The formation of reactive oxygen species (ROS), the composition of the carrier gas, the frequency of plasma irradiation, and the virulence of the bacterial strain all play a major role in the mechanism of plasma-based sterilization. Plasma irradiation has been shown to be more successful than non-thermal treatments like UV sterilization since it leaves no residue. It has a number of advantages, including the reduction of toxic residue, reduced chair-side time, and the ability to be used on moisture-sensitive devices [20]. After irradiation with atmospheric pressure non-thermal air plasma, the colony forming units of both *E. coli* and *B. subtilis* on diamond burs and silicone impression materials were drastically reduced. Cross-contamination between the dental instruments and the patients and transmission of infection from dental impressions to the lab technicians can be prevented by exposure to high-intensity plasma free radicals [21, 22].

6.1.6 ENHANCING ADHESIVE QUALITIES:

Adhesion is the key factor that enhances the clinical performance of composite resins [23]. When the adhesive spreads spontaneously across the entire adherend surface, it achieves optimal adhesion with good wettability. Plasma irradiation enhances adhesive bonding by creating micro-structural and chemical modifications on the etched enamel and dentin surface, forming a thin plasma coating that improves bonding with composites. Atmospheric cold plasma brush (ACPB) treatment can enhance adhesive qualities [24, 25].

6.2 DIRECT APPLICATIONS:

6.2.1 MICROBIOCIDAL ACTION:

Dental caries, gingival and periodontal disorders, and oral mucositis are all caused by biofilms that grow on the tooth surface [26]. These biofilms can cause peri-mucositis and peri-implantitis, damaging dental implants. NTP has the capacity to eradicate biofilm matrix without damaging the oral tissue, with minimal heat transmission to the dental pulp. In an in-vitro investigation by Koban et al., NTP was more effective than chlorhexidine in eliminating bacteria in the dental biofilm [27]. The lipid bilayered bacterial cell membrane is composed of unsaturated fatty acids and proteins, both of which are engaged in transport processes across the membrane. The unsaturated fatty acids in the cell are vulnerable to the action of hydroxyl ions in NTP irradiation [28].

6.2.2 DENTAL CARIES :

Plasma has the ability to sterilize uneven surfaces, making it ideal for disinfecting carious lesions without the need to use dental burs [29]. Plasma releases free radicals that aid in bacterial decontamination with minimal tissue damage. Govil et al. investigated the interactions of plasma with dental tissue via the use of a plasma needle. Plasma irradiation reaches the entire depth of the prepared cavity very easily. Firing low plasma temperature beams on dentin reduces the amount of caries-producing bacteria [30].

6.2.3 CAVITY PREPARATION:

Cold plasma is known for its potential applications in dentistry because it is vibration-free and reduces pain[31]. That is especially useful for anxious patients fearful of the drill employed for cavity preparation. Plasma has the ability to disinfect cavities in carious lesions [32]. Eva Stoffels' proposed plasma irradiation through plasma needles has a bacteriocidal effect on Escherichia coli, causing cell wall membrane lysis and bacterial DNA damage [33].

The advantages of the plasma needle compared to conventional cavity preparation include the following: bacteriocial action; minimal tooth preparation, preventing bulk removal of tooth structure; easy access and disinfection of small pit and fissure carious lesions; and low temperature of operation; thereby temperature increase in the pulp is prevented.

Park et al. discovered that an argon plasma brush could effectively deactivate Streptococcus mutans in 15 seconds and Lactobacillus acidophilus in 5 minutes [34].

6.2.4 ROOT CANAL DISINFECTION:

The root canal system is known for its anatomical complexities such as accessory canals, lateral canals, isthmuses, ramifications, apical deltas, canal curvatures, etc. It has been reported that bacteria such as *Enterococcus faecalis* can invade the dentin tubules up to 1000 m in depth. The task of eliminating persistent microorganisms, particularly within the biofilm, is complex, and clinical trials have shown that traditional disinfection techniques result in recurrent endodontic infections and failure of primary endodontic therapy [35,36]. In an in-vitro investigation, Pan et al. demonstrated that cold plasma had greater effectiveness in eliminating *E. faecalis* biofilms [37].

NTP, in the gaseous state, penetrates deep into the complex root canal system, making direct contact with bacteria, which is impossible with the traditional approaches of cleaning and shaping. According to several studies, ROS appears to be the most important factor in bacterial inactivation. Using a medical syringe and a needle, Lu et al. created the "Model RC-1" plasma jet apparatus. An 8 kV, 500 ns pulsed direct current with a pulse frequency of 10 kHz was used to power the device. At a flow rate of 0.4 slm, a gas combination of 80 % He and 20 % O_2 was injected into the syringe. The needle, which had an inner diameter of 200 m, was used as the electrode. Hence, the needle could be easily inserted into the root canal system to generate a very narrow plasma plume, producing effective root canal disinfection [38].

6.2.5 TOOTH WHITENING:

Bleaching with hydrogen peroxide (H_2O_2) is one of the treatment procedures performed in regular clinical dental practice. NTP is recommended for teeth bleaching.

Lee et al. proved that NTP irradiation resulted in the release of hydroxyl radicals and removed the surface proteins, thereby improving the efficacy of H_2O_2 [39].

Park et al. proposed the application of a low-frequency plasma source along with H_2O_2 to remove intrinsic stains [40]. Kim et al. [41] employed liquid plasma generated by a radio frequency (RF)-driven gas, referred to as a liquid hybrid plasma system. When compared to traditional light sources, Hamid et al. proved that NTP in combination with 15% carbamide peroxide and 5.4% H_2O_2 was more effective in tooth bleaching without producing thermal damage to the underlying pulp [42].

6.2.6 ORAL ONCOLOGY:

In addition to surgical techniques, smart drug delivery systems (SDDSs) and stereotactic body irradiation have been proposed for oral cancer therapy. Immunotherapy has also progressed significantly in recent years. The recent discoveries, on the other hand, employ sophisticated equipment and ultra-expensive medications. As a result, searching for alternatives is required.

The application of CAPP in oral oncology is due to its ability to generate ROS and RNS, causing selective destruction of malignant tumour cells [43].

The importance of oxidation/reduction potential in the course of the disease process is well established due to the HOCl or NO/ONOO signalling pathways. NO and nitrite therapies are used as anti-cancer agents as a result of their effects on cancer cells and catalase-dependent apoptotic pathways, which are implicated in disease progression and regression [44,45].

A list of the functions of the CAP mechanisms in cancerous cells:

1. Activating P53
2. Activating inhibitor, P21CDK
3. Cell cycle arrest occurs at the G2/M and S phases.
4. release of ROS, DNA destruction, and prevention of cell replication.
5. stimulating apoptosis through mitochondrial ROS production and turning the mitochondria
6. A decrease in mitochondrial membrane potential, mitochondrial enzyme activity, and cellular respiration in cancerous cells.
7. Changes in the concentrations of ROS, NO, and intracellular fluid lipid peroxide.

According to Han et al. [46], N2-CAPP caused DNA damage in SCC-25 oral cancer cells. This was also effective in the treatment of head and neck squamous cell carcinoma (HNSCC) [47]. CAPP can also be used to treat oral lichen planus, which is a precancerous lesion. Research revealed that cancer cells like SCC-15 and HNSCC were more sensitive to CAPP.

6.2.7 TREATMENT OF ORAL CANDIDIASIS

Oral candidiasis is a common opportunistic infection in immunocompromised patients. Refractory cases of oro-pharyngeal candidiasis are becoming more common, and treatment of these cases is more challenging due to antifungal resistance. Proton ATPases, efflux pumps, adhesion, morphogenesis, and oxidative stress resistance have all been identified as new targets for antifungal drug development. CAPP had antifugal modulatory effects on Candida albicans virulence factors such as adhesion, filamentation, and reduction of ergosterol production, which were scientifically proven in vivo in a mouse model [48].

7. LIMITATIONS:

CAP is a new technology, but it has limitations, and the equipment's safety is of paramount importance.

1. There is difficulty in portability and transporting the instrument for dental use.
2. high technical sensitivity.
3. Efficiency is compromised by the old previous amalgam restoration.
4. Spores cannot be inactivated due to the limited depth of penetration of cold plasma.
5. The high cost of the equipment, challenges in marketing, difficulties in maintenance and availability are some of the issues of major concern.

8. CONCLUSION:

The scope of CAP in dentistry is enormous due to its multiple applications and microbicidal properties. It can be employed in almost all branches of dentistry, being painless, drill-free, and patient-friendly. Amidst its various biomedical applications, plasma therapy has also been effectively administered for the treatment of COVID-19 [49,50]. However, further investigations are necessary to gain in-depth knowledge about the mechanism of action and biological plasma-cell interactions.

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