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The Role of Carbon Dots in Combatting Oral Diseases: Insights and Perspectives

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ABSTRACT: Carbon-based nanomaterials with a particle size of less than 10 nm are known as carbon dots (CDs). It is well recognized that these nanoparticles have a wide range of applications in the field of innovative drug delivery for conditions including cancer, infectious diseases, ocular illnesses, and brain disorders. CDs possess biocompatibility, eco-friendliness, ease of synthesis, and reduced cytotoxicity. Additionally, they exhibit exceptional chemical inertness, rendering them highly suitable as nanocarrier systems for the potential delivery of multifunctional drugs. Currently, a large number of researchers worldwide are studying CD-based drug delivery systems to evaluate their efficacy and versatility in the pharmaceutical industry. As a result, our understanding of the physicochemical properties, diagnostic potential, and drug delivery features of CDs has significantly advanced. The design and development of a theranostic system based on CDs for the treatment of numerous illnesses has been spurred by this progress. The subject of nanotechnology has advanced significantly in recent years, especially in the fields of dentistry and medicine. The application of nanotechnology in the field of periodontics is known as nano periodontics. Nanoscale materials are superior to typical materials in terms of their qualities and performance, which makes them very useful in many different disciplines such as medication administration, therapy, diagnosis, prevention, and dental implant coatings. Our goal in writing this paper is to provide an overview of the prospective uses of CDs in the future for several applications related to oral and periodontal health, particularly as a drug delivery system using nanocarriers.

1. INTRODUCTION

In 2004, Walter Scrivens and associates made an inadvertent discovery on the characteristics of carbon dots (CDs) while producing single-walled carbon nanotubes (Xu et al., 2004). Excellent photostability, biocompatibility, adaptability, low cytotoxicity, high chemical inertness, simple synthesis, environmental friendliness, no-blinking photoluminescence, and enhanced water solubility are some of these qualities. CDs are carbon clusters that are either amorphous or nanocrystalline, with sp2 or sp3 configurations. These clusters have functional groups attached to their surfaces. Typically, their diameter is less than 10 nm. CDs can be categorized into three main types: carbon quantum dots (CQDs), carbon nanodots (CNDs), and carbonized polymer dots (CPDs) (Koutsogiannis et al., 2020).Carbon nanodots (CNDs) demonstrate significant quantum confinement and edge effects, which play a crucial role in determining their optical characteristics. By changing their size, surface functional groups, and synthesis techniques, these characteristics may be

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changed. The aforementioned features make CDs ideal for use in a variety of fields, including as bio-imaging, optoelectronics, and drug delivery systems (Ren et al., 2019).When it comes to drug administration for a variety of conditions, such as cancer, ophthalmic illnesses, infectious diseases, neurological disorders, and gene delivery, CDs are predominantly used as nanomaterials in the pharmaceutical industry (Z. Zhang et al., 2019). CDs' surfaces are functional groups that increase their water solubility and make it easier for them to conjugate with different organic and inorganic polymers and biomolecules, allowing for a variety of uses (Singh et al., 2017).Additional alterations that improve CDs' target ability, sensitivity, optical properties, and selectivity are facilitated by the presence of functional groups on their surface, such as amino, carboxyl, and hydroxyl groups. (Xu et al., 2016)

The utilization of CDs offers the benefit of enabling the selection of surface functionalities through electrostatic interactions for the purpose of targeting specific drug molecules (Singh et al., 2017).So far, several CD categories have been developed for a wide range of applications, including as bio imaging, drug delivery for therapeutic purposes, bio sensing, targeting of the drug, chemical sensing, and delivery of the gene, electrolysis, and more. Furthermore, researchers have discovered that CDs produce light in the near-infrared (NIR) spectral area when they are subjected to NIR light. This finding broadens the potential applications of CDs in various fields such as drug delivery, bioimaging, photoacoustic imaging, and anticancer treatment. CDs possess exceptional photostability and fluorescence characteristics, rendering them suitable for application as probes in the analytical domain (Xu et al., 2016) and for the purpose of characterizing normal cells and cancer cells using bioimaging techniques (An et al., 2021; Zeng et al., 2016).

Oral diseases are a significant public health concern, impacting a substantial number of individuals world-wide and diminishing their overall well-being. Periodontal disease is a comprehensive term encompassing the inflammatory condition affecting both the gingiva (gingivitis) and/or periodontium (periodontitis). The progression of the disease unfolds from gingivitis to periodontitis. In its initial stage, called gingivitis, the gingiva becomes swollen, red and may bleed. This gingival inflammation can subsequently extend to involve the periodontal attachment apparatus and lead to alveolar bone destruction (K. Bhavikatti et al., 2024; Pizzorno et al., 2015). In addition to affecting 20–50% of the population, periodontal disorders are the main cause of tooth loss in both developed and developing nations (Nazir, 2017).

Inflammation and the loss of the periodontal attachment system in adults and adolescents are hallmarks of the severe types of periodontal disease known as periodontitis. Periodontal pocketing, gingival inflammation, loss of alveolar bone, and attachment loss are the hallmark symptoms of periodontitis (S.K. Bhavikatti et al., 2021). Even with careful dental treatment, some people still experience periodontal disease. This could be because the disease-causing pathogens enter the periodontal tissues and cause periodontal pockets, or they could be living in furcations or other tooth structures where they are not accessible by periodontal instruments, or it could be because the host's defence mechanisms are compromised.

The goal of periodontal treatment is to eradicate etiological bacteria and their by-products in order to produce a root surface that is "biologically acceptable." (Spellberg et al., 2013). The cornerstone for treating and preventing periodontal disease is mechanical debridement, which includes scaling and root planing. Chemical plaque management techniques can also be used as adjuvants to sustain long-term effects. Chlorhexidine gluconate is the most widely used and researched chemical plaque control agent. Because it possesses the majority of the characteristics of the perfect antimicrobial solution, including substantivity and a wide spectrum of action, it is regarded as the gold standard plaque control agent. Long-term usage of chlorhexidine mouthwash has been linked in studies to a number of negative consequences, including tooth discoloration, taste loss, degeneration of the tongue papilla, and in rare instances, parotid edema (McCoy et al., 2008)

Previous research has demonstrated the significant anti-inflammatory, antioxidant, and antibacterial properties of CDs derived from herbal sources (Ghirardello et al., 2021; Rodríguez-Varillas et al., 2022; Sharma et al., 2023). Nevertheless, there is a lack of documented evidence about the utilization of green-synthesized CDs for biomedical applications in the treatment of oral or periodontal diseases. There is paucity of literature regarding the applications of carbon dots for oral and periodontal implications. Therefore, this review emphasizes on the oral and periodontal health applications of CDs, especially as a drug delivery system which could potentially lead to unique ramifications in the future.

2. SYNTHESIS OF CDS

In 2004, Xu et al. accidentally synthesized the first CDs while attempting to purify single-walled carbon nanotubes using arc-discharge soot. Gel electrophoresis was employed to separate soot suspension components, unveiling a new fluorescent material. Chemical and physical methods such as heat treatment, electrochemistry, arc discharge, hydrothermal or acidic oxidation, ultrasonic treatment, plasma therapy, and laser ablation are used to create CDs. Top-down and bottom-up syntheses are the two main categories into which CD preparation techniques fall. Top-down approaches use processes like chemical oxidation, laser ablation, and hydrothermal cutting to break down big carbon sources into tiny pieces. Bottom-up methods employ techniques like ultrasonication, microwave pyrolysis, and direct thermal decomposition to carbonize organic precursors, including natural gas or carbohydrates, in order to produce CDs. Post-synthesis, various techniques like centrifugation and dialysis chromatography are employed to achieve uniformity.

The morphology and structure of CDs largely rely on factors like the precursor, preparation method, and experimental conditions. Top-down methods, using source materials like graphite powder, graphene nanosheets, or coal, result in CDs with varying diameters, heights, and structures. Techniques like etching with UV irradiation or hydrothermal treatments yield different outcomes. Top-down CDs often have spherical or sheet shapes, are less than 10 nm in size, and are shorter than 3 nm in height. Although bottom-up CDs are often stacked with heights less than 10 nm, they also have diameters below 10 nm (Setiawatie et al., 2021).Because of its affordability and ease of use, hydrothermal synthesis is the most widely used green carbon CD production technique. This process utilizes pressurized autoclave containers, temperatures between 120 and 240°C, and reaction durations ranging from three to twelve hours. It can also employ water or safe organic solvents like ethanol. High temperatures and extended response times are necessary, but the settings may be set to maximize performance and yield while consuming the least amount of energy. On the other hand, microwave synthesis produces results more quickly by directly heating reaction mixtures for a few minutes with an 800W microwave power. It is more costly despite its advantages since specialist equipment is required. But compared to hydrothermal synthesis, this technique may be more energy-efficient and yield results more quickly (Chahal et al., 2021)

Green CD synthesis uses a variety of plant components, including leaves, flowers, and roots, as renewable carbon sources. Shells, kernels, bark, stalks, and peels are examples of additional plant biomass that can be utilized. Preprocessing is required for these feedstocks in order to reduce particle size and eliminate extra water. One energy-efficient way to dehydrate is by solar drying. An easy "ready-to-use" option for hydrothermal synthesis is to employ apple juice; this eliminates the need to re-disperse dried plant materials in water. But using this approach lessens the variety of carbon in the dry feedstock (Chahal et al., 2021).Ginger juice (20 ml) was hydrothermally processed at 300°C for two hours, producing a black carbonized solution, in order to facilitate the green synthesis of carbon dots. Large particles were removed by centrifuging and filtering it after it cooled. Using a dialysis membrane, the resultant brownish-yellow supernatant (18 ml) was dialyzed in ultrapure water for two hours, changing the water every half an hour. After the concentrated CDs solution was freeze-dried, a concentration of 11.1 mg/ml was obtained (C.L. Li et al., 2014).

3. CHARACTERIZATION AND PROPERTIES OF CDS

3.1. UV-Visible (UV-Vis) Spectroscopy

The fundamental idea behind UV-Vis spectroscopy is the absorption of light in the visible (200–400 nm) and ultraviolet (400–800 nm) light ranges by various chemical substances**.** The technique relies on the interaction of light with matter at electronic levels, where chromophores present in compounds absorb specific wavelengths of light, causing electrons'transition to higher energy states. The material can be subjected to both qualitative and quantitative investigation using the generated absorption spectrum (Tissue, 2012). UV-Vis Spectroscopy of CDs synthesized from ginger juice has shown a strong absorption peak at 285 nm, attributed to the π-π^* transition of C=C bonds, and a weaker peak at 340 nm, ascribed to the n-π^* transition of C=O bonds. This observation indicated the presence of sp2-hybridized carbon domains in the CDs (C.L. Li et al., 2014)

3.2. Fourier Transformer-Infrared (FT-IR) Spectroscopy

A popular analytical method called FT-IR spectroscopy works on the basis of the idea that molecules vibrate when they absorb infrared light at particular wavelengths. This absorbed radiation corresponds to the vibrational energy levels of the molecular bonds within the sample. FT-IR measures the absorption of infrared radiation as a function of wavelength, which is then converted into a spectrum using a mathematical technique called Fourier transformation. The resultant spectrum enables researchers to identify functional groups and molecular structures by providing comprehensive information on the sample's chemical makeup, structure, and reactions (Fadlelmoula et al., 2022).

A study revealed that, FTI-R provided insights into the functional groups present on the CDs surface. The observed bands corresponded to O-H stretching (3300-3500 cm-1), C-H stretching (2850-2950 cm-1), C=O stretching (1630 cm-1), and C-O stretching (1000-1300 cm-1). These results indicated the presence of hydroxyl, carboxyl, and carbonyl groups on the CDs surface, which could contribute to the surface passivation and water solubility of the CDs (C.L. Li et al., 2014).

3.3. Zeta Potential and Dynamic Light Scattering (DLS)

The stability and charge of colloidal dispersions are evaluated using the zeta potential approach. Strong repulsive forces between particles are indicated by high zeta potential values, which can be either positive or negative and result in a stable dispersion. In contrast, low zeta potential values suggest weak repulsive forces and a higher likelihood of particle aggregation, resulting in an unstable dispersion (Shaw, 1992). DLS analyses the variations in scattered light intensity brought on by the Brownian motion of the sample's particles to determine the size distribution and zeta potential of CDs. A straightforward one-pot approach was utilized to produce highly luminous CDs at 240°C for a study that examined the DLS and zeta potential of CDs. These particles' DLS and zeta potential were measured using a Malvern Zetasizer Nano series, Nano-ZS90 device. The size distribution of the CDs was ascertained using DLS graphs, and the surface charge and stability of the CDs in the solution were ascertained using zeta potential graphs (Hoan et al., 2019).

3.4. Optical Properties of CDs by Fluorescence Profiling

CDs exhibit considerable UV absorption that may sometimes extend into the visible spectrum. Fluorescence profiling of CDs measures the emission spectra of the sample upon excitation with a specific wavelength of light. The absorption spectral area may continually readily shift after change of some passivating chemicals. The main luminescence characteristics of CDs are photoluminescence and electrochemical luminescence, with photoluminescence being the most noticeable performance. High fluorescence stability, nonblinking, tunable excitation, and emission wavelengths are only a few of the great optical features of CDs, which play a significant role in nearly all fluorescent nanomaterials applications. CDs' unclear emission processes, however, merely serve to maintain the phenomenon's current levels (Mansuriya & Altintas, 2021).

3.5. X-ray Diffraction (XRD)

XRD is a technique that determines the crystal structure and phase of a sample by analyzing the diffraction pattern of X-rays scattered by the sample's atoms. A study revealed that XRD was conducted to study the crystal structure of the synthesized nanoparticles and confirm the successful coating of CDs over the titanium di-oxide nanoparticles. The XRD results have revealed that the synthesized nanoparticles exhibited a crystalline anatase phase of titanium dioxide, with characteristic peaks at 25.3°, 37.8°, 48°, 53.9°, 55°, and 62.7°. The (101), (004), (200), (105), (211), and (204) planes were the locations of these peaks, which showed that the carbon dots had been effectively coated over the titanium dioxide nanoparticles. A large rise at around 23° further supported the presence of carbon dots and was linked to the amorphous character of CDs (Sawant et al., 2016).

3.6. Scanning Electron Microscopy (SEM)

SEM produces a high-resolution picture of the surface morphology and structure of a material by scanning its surface with a focussed electron beam. This process produces secondary and backscattered electrons. SEM can effectively capture high-resolution images of CDs for characterization purposes. CDs are subjected to a high-energy electron beam. This leads to an accumulation of charge, producing an image that offers comprehensive details on their shape, topography, chemical makeup, granular orientation, and crystallographic data (Sharma & Das, 2019).

3.7. High Resolution Transmission Electron Microscopy (HR-TEM)

HR-TEM uses an electron beam to pass through the sample in order to study the size and phase of CDs at the atomic level. The characteristics of CDs made from ginger were examined using a variety of characterisation methods. The produced CDs were spherical in form, with an average diameter of around 3.6 nm, and a size distribution of 2–6 nm, according to transmission electron microscopy (TEM). HR-TEM demonstrated the existence of lattice fringes, confirming the crystallinity of the CDs, and further validated the spherical shape (C.L. Li et al., 2014).

3.8. Atomic Force Microscopy (AFM)

AFM is a technique that measures the surface topography of a sample by scanning a sharp probe over the surface and detecting the force interactions between the probe and the sample. The CDs were characterized by various methods in a study including AFM, which provided high-resolution images of the nanoscale structures. The AFM analysis of the as-synthesized CDs reveals the presence of individual particles and small aggregates (<100 nm) with average height measurements of carbon dots in the sample (Ventrella et al., 2020).

4. BIOMEDICAL PROPERTIES OF CDS

The antioxidant capacity of CDs was evaluated using the DPPH radical scavenging method. The electrochemical study focused on the changes of redox peaks of the oxidation of DPPH● at gold electrodes with the addition of carbon nanodots. Existing research provides valuable insight into the antioxidant properties of carbon nanodots (W. Zhang et al., 2017). This suggests that CDs may be considered as potential antioxidants, although their efficiency varies compared to traditional antioxidants like Ascorbic acid (Rodríguez-Varillas et al., 2022). The comparative analysis underlines the need for further exploration of CDs' antioxidant properties, especially regarding their application as an antioxidant in dental field.

The potential biological uses of CDs, such as their ability to scavenge free radicals and exhibit antioxidant and in vitro anti-inflammatory properties, were studied. Research was conducted using membrane stabilization for anti-inflammatory efficacy, phosphomolybdate for antioxidant activity, and DPPH for free radical scavenging. The results imply that CDs may prove to be effective therapeutic agents in a range of biological contexts (Gudimella et al., 2022).

In an update since 2019, the authors reviewed the latest research on four types of antimicrobial CDs: nitrogen-doped, metal-containing, antibiotic-conjugated, and photo-responsive. CDs have demonstrated significant antibacterial activity against various bacteria, including Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, and Bacillus subtilis, among others, highlighting the promising antimicrobial properties of CDs (Lin et al., 2022).

CDs may be considered as potential antioxidants, although their efficiency varies compared to traditional antioxidants like Ascorbic acid (Rodríguez-Varillas et al., 2022). The comparative analysis underlines the need for further exploration of CDs' antioxidant properties, especially regarding their application as an antioxidant in various fields.

There is a growing body of literature emphasizing the role of CDs in mitigating inflammation, suggesting their potential applications in inflammatory conditions (Kong et al., 2022; Sharma et al., 2023). However, the comparative analysis underscores the necessity of optimizing CDs for enhanced anti-inflammatory effects and evaluating their performance against standard anti- inflammatory drugs.

4.1. Antimicrobial Activities of CDs

The majority of pathogenic bacteria that cause oral infectious illnesses are found in the mouth cavity. These microbes frequently form biofilms on several oral cavity surfaces, including supra- and sub-gingivally CDs' unclear emission processes, however, merely serve to maintain the phenomenon's current levels (Ahmed et al., 2022; Karobari et al., 2021; Kolenbrander et al., 2010). Dental caries is commonly associated with supragingival plaque that negatively affects the oral hard tissue. Further development of this disease may lead to infection of the pulp tissue as well as the periapical area (Larsen & Fiehn, 2017) There is a common correlation between subgingival plaque biofilms and periodontitis (Takeuchi et al., 2011).According to (Preshaw et al., 2004), deterioration of the soft and hard tissues in the mouth, such as the alveolar bone and periodontal ligament, is one of the condition's possible outcomes.

CDs differ from antibiotics due to their complex antimicrobial activities, which include breakdown of bacterial membranes (P. Li et al., 2020), generation of reactive oxygen species (ROS) (Romero et al., 2021), and interruption of protein synthesis (Zhao et al., 2022). These processes allow CDs to effectively combat drug-resistant bacteria, including multidrug-resistant (MDR) strains, and to sterilize quickly in only a few minutes (Y.J. Li et al., 2016; Sidhu et al., 2017; Yang et al., 2021; Zhao et al., 2022). Moreover, previous research has demonstrated that CDs exhibit favourable permeability and has the potential to efficiently eliminate oral biofilms (Liang et al., 2020; Pourhajibagher et al., 2019). It is vital to note that, CDs possess significant benefits in penetrating the narrow regions of the periodontal pockets due to their minuscule particle size.

Tang et al. clearly synthesized CDs made from fucoidan (FD). As per the findings (Tang et al., 2022), the FD-CDs demonstrate the capacity to efficiently enter dentin tubules and eradicate E. faecalis from both root canals and dentin tubules. The antibacterial qualities of NaClO are similar to this effectiveness. The aforementioned example demonstrates the significant benefits of CDs in the removal of oral biofilms. CDs have also demonstrated a significant efficacy in combating intracellular bacteria and fungi, as evidenced by studies conducted by (Ardekani et al., 2019; X. Li et al., 2019). Their optical features have led to extensive research in the field of microbial imaging (Lin et al., 2022;) (Xu et al., 2016).

CDs have a lot of surface area, a high degree of biocompatibility, great water solubility, and a quick rate of drug loading. These qualities make them appropriate delivery systems for antimicrobial agents, including antibiotics and medications with controlled release (An et al., 2021). Additionally, research has shown that modified CDs have the potential to augment the antibacterial properties of antibiotics. Research by Thakur et al. (2014) has shown that ciprofloxacin and CDs were made from gum arabic coupled to produce a compound known as Cipro@Cdots. Due to this conjugation, the antibacterial activity against both Gram-positive and Gram-negative bacteria was increased (Thakur et al., 2014). Similarly conjugates including herbal derivatives incorporating CDs need to be explored as safe alternatives in the management of oral and periodontal disease.

Pseudomonas gingivalis, the predominant bacterium responsible for periodontitis, has been extensively documented to infiltrate the cells of the oral epithelium, evading the immunological response of the host and developing resistance to antibiotics (Xiong et al., 2012; Ye et al., 2017). According to (Miramoth et al., 2012), +the persistence of the pathogen results in the reoccurrence of infection. However, it is important to remember that commonly used antibiotics have limited cellular penetration, which calls for the creation of novel intracellular antibacterial drugs CDs' unclear emission processes, however, merely serve to maintain the phenomenon's current levels (Abed & Couvreur, 2014). The results of research show that CDs are both biocompatible and capable of being absorbed by cells (L. Li et al., 2023). The previously described studies set a need for the application of CDs in the fight against oral intracellular microbes.

Carbon dots (CDs), particularly graphene quantum dots (GQDs) derived from graphite, have been utilized to enhance the antimicrobial properties of curcumin (Cur) in forming nanocomposites (GQD-Cur). This combination has been tested against perio-pathogenic mixed biofilms, including A. actinomycetemcomitans, P. gingivalis, and P. intermedia, to assess its antibiofilm capabilities. The results indicated that under blue light-emitting diode (LED) exposure, GQD-Cur nanocomposites increased reactive oxygen species (ROS) generation, showcasing a significant inhibitory effect on these mixed biofilms via a process known as antimicrobial photodynamic therapy (aPDT). The study demonstrates how CDs can be a promising tool in combating biofilm-related oral infections by enhancing the antimicrobial efficacy of existing treatments (Pourhajibagher et al., 2019).

5. FUTURE IMPLICATIONS OF CARBON DOTS

- **In-vivo Studies:** Future research should focus on in-vivo studies to validate the cytotoxicity findings in a more complex biological context. Animal models can provide insights into safety and efficacy, helping bridge the gap between in-vitro and clinical applications.
- **Long-term Effects:** Investigating the long-term effects of CDs on oral cells and tissues is crucial. This could involve extended cytotoxicity studies, histological assessments, and monitoring for potential chronic effects.
- **Mechanistic Studies:** Understanding the mechanisms underlying the cytotoxic effects of CDs is vital. Molecular and cellular studies can reveal the pathways involved, helping identify potential targets for therapeutic interventions.
- **Optimal Concentration Determination:** Future studies should explore a broader concentration range to identify the optimal and safe concentration of CDs for various applications, including oral care products and oral wound healing.
- **Comparative Clinical Trials:** Clinical trials comparing NEG-IS-based oral care products with conventional products, such as CHX, would provide valuable data on their efficacy and safety profiles in real-world settings.
- **Formulation Development:** Further research can focus on developing specific formulations of mouthwash,

toothpaste, or gels that incorporate CDs effectively while maintaining its safety and therapeutic properties.

- **Exploration of Other Applications:** Future research can explore the pharmacological and therapeutic potential of CDs in other areas of healthcare and wellness.
- **Standardization:** Efforts should be made to standardize the production and composition of CDs to ensure consistency in its safety and efficacy across different products and manufacturers.
- **Interdisciplinary Research:** Collaborations between dental professionals, pharmacologists, and biotechnologists can provide a holistic approach to understanding the clinical and therapeutic potential of CDs.

6. CONCLUSION

The consequences of the developing carbon dots for oral health are discussed in this scoping review. In the area of dental health, carbon dots (CDs) show a great deal of promise as potential antibacterial, anti-inflammatory, and antioxidant agents. Future research on CDs' involvement in periodontics, particularly their ability to combat periodontal infections with antibiotics, must be thoroughly examined. It is necessary to investigate their cytotoxicity towards human gingival fibroblasts in order to safely use them in innovative nano-formulations that contain CDs.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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All authors have read and agreed to the published version of the manuscript. Conceptualization: S.K.B., S.L.Z., R.B.R and P.B.D., Manuscript Writing: S.K.B., M.K and M.I.K., Proof reading and editing: M.K., S.K.B and M.I.K.

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