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Proflavine an acridine DNA intercalating agent and strong antimicrobial possessing potential properties of carcinogen

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Abstract

Proflavine finds a wide array of applications in clinical, therapeutic, industrial and cutting edge research. This study investigates properties of proflavine and brings out its current status based on overall merits and demerits. Review was carried out starting from late 1800s to 2017 about all aspects of proflavine. We have accessed digital libraries in University of Cambridge, Oxford University, Harvard University and Massachusetts Institute of Technology through their institutional repository software. Popular open source solutions like DSpace, EPrints, Digital Commons, Fedora Commons, Islandora and Hydra were included. Proflavine finds many applications including as an anti microbial agent and often used as a topical agent. This compound denatures bacterial DNA leading to lysis of bacteria. Due to its intercalating property it affects host DNA, which has potential chances to induce skin cancer and other malignancies. Reactive oxygen species (ROS) released by proflavine play a crucial role in denaturing host DNA. Proflavine can penetrate beyond epidermal and dermal structures and accumulate in cell nuclei. In human cell culture proflavine is known to be taken up by many kinds of cells and is concentrated in the nuclei. Our studies revealed that despite its oncogenic potential, proflavine currently finds its applications in therapeutic, diagnostic and in research not alone in developing countries but also in developed countries. Proflavine exhibited wide potent activity against various groups of microorganisms. After exposure in human skin proflavine alters the structure of epidermal DNA strands leading to mutation. Many industrial workers, researchers, health care professionals are exposed to proflavine in enormous amounts daily through oral, respiratory and cutaneous routes. We conclude that even though proflavine has strong antimicrobial and other uses due to its carcinogenic nature, we recommend that it is time to rethink the use of this compound and to search for good alternative replacement.

Keywords: Proflavine; DNA damage; Free radical; Antimicrobial; Carcinogen

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1. Introduction

Cancer plays a crucial role in causing severe morbidity and enormous mortality throughout the world. Many types of these cancers are induced by toxic chemicals, biological compounds and microorganisms. The major mechanism of oncogenesis in human body is due to alteration or insertion of genes in the normal host DNA, thus leading to mutation of genetic material. There are so many cutaneous diseases caused by microorganisms like Gram positive, Gram negative bacteria, fungi, parasites and some viruses. For therapeutic use proflavine is often used as topical antiseptic agent as well as a disinfectant. In other sectors like industries, laboratories workers are exposed to proflavine by various ways.

Proflavine, an acridine dye is a known DNA intercalating agent. Proflavine, an acridine dye with a flavine nucleus can penetrate the epidermal and dermal structures in the in vivo stained cells and accumulate in the cell nuclei, only cells of the central nervous system did not absorb any proflavine [1]. In human cell culture also, proflavine is known to be taken up by many kinds of cells and is concentrated in the nuclei [2]. Proflavine is a strong DNA intercalating agent. The generation of reactive oxygen species (ROS) by photo excited proflavine is reported in presence of a macromolecule in the reaction [3]. Proflavine when excited with visible light can induce DNA strand cleavage [4]. Piette et al. have shown the production of ROS from proflavine [5] that causes base modification and strand breaks in DNA [6]. Replication of DNA at this stage leads to mutation or apoptosis [7].

Riboflavin (vitamin B_2) is structurally similar to proflavine; proflavine has an amino group while riboflavin has a ribityl group in the side chain structure. Earlier studies from our laboratory have shown that riboflavin generates superoxide anion in visible light and the rate of formation of superoxide anions is stimulated in the presence of double stranded DNA [8]. Another study has also shown that riboflavin causes breakage of calf thymus and super coiled plasmid DNA [9] and hemolysis of red blood cells [10]. Photoilluminated riboflavin also causes protein degradation. This degradation is enhanced when a transition-metal ion, such as Cu (II), is present in the reaction with riboflavin [11]. This protein degradation is preceded by the binding of riboflavin to the protein at or around tryptophan residues. Photo illuminated proflavine, like riboflavin, can lead to production of ROS in the human body.

In the present scenario, proflavine is widely employed in various circumstances including biomedical applications. Even though proflavine has potential antimicrobial properties on the other hand it exhibited toxic effects on protein, DNA and many enzymes. This study is extremely vital and its findings may be applied in the understanding of morphogenesis of the cell, sub cellular degeneration, cellular DNA auto degradation, cellular aging, anti-aging process, cellular oncogenesis and mechanism of action of potential carcinogens. So these findings of this study directly or indirectly help oncologists, cellular biologists, biochemists, pathologists and embryologists in understanding the biological effects, biochemical impacts and its protein degradation of oxygen free radicals generated by proflavine.

2. Methods

Detailed study with review of literature was carried out starting from the year late 1800s from the discovery of proflavine until the recent developments on proflavine in February 2017. All aspects of proflavine were included for this study. Particular emphasis was given to know about: a) Nature of proflavine, b) Mechanism of action of proflavine, c) Properties of proflavine, d) Action of proflavine on microorganisms, e) Action of proflavine on DNA and enzymes, f) Proflavine and its carcinogenic potential.

We have accessed digital libraries in University of Cambridge, Oxford University, Harvard University and Massachusetts Institute of Technology through their institutional repository software. Data searching was carried out from archived and organized contents of the respective libraries. Popular open source solutions like DSpace, EPrints, Digital Commons, Fedora Commons, Islandora and Hydra were included. 500 potential set of literature were selected and 100 appropriate articles were identified for this study based on convenience sampling.

3. Results

3.1. Interaction with nucleic acids

The nature of the interaction of acridine derivatives, especially aminoacridines, with nucleic acids has attracted increasing attention since their earliest use as cellular stains. The widespread biological effects of acridine derivatives gradually came to be connected principally with their ability to interact with nucleic acids, but interest in this interaction was heightened

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