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Nanocarriers as a drug delivery vehicle for skin carcinoma: A Review

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ABSTRACT

One of the most prevalent cancers that affects a large population and has a high morbidity rate is skin cancer. Globally, researchers have tried to identify a new chemical entity by using variety of drug and novel drug delivery systems with minimum side effects. But there is still no drug on the market that is effective enough to treat the skin cancer. Current therapeutic techniques emphasise surgery, radiation, immunotherapy and chemotherapy, which gradually cause destruction of unaffected cells. Additionally, utilising chemotherapy drugs can cause cancer cells to develop drug resistance and change their target site. The use of nanocarriers for skin cancer therapies, such as liposomes, solid lipid nanoparticles, nanostructured lipid carriers, niosomes, and ethosomes, etc. has demonstrated significant results. This review covers diverse forms of skin cancer, its types, various nanocarriers, and therapeutic uses of drug-loaded nanosystems for skin cancer.

KEYWORDS: Skin cancer, UV radiation, Melanoma skin cancer, Non-melanoma skin cancer, Nanocarrier.

I. INTRODUCTION

In the human body, skin is the biggest organ. It comprises 16% of the body's total mass and has a surface area of roughly 1.8 m2. Pathogens cannot enter the body through this barrier, which also serves as a sensory organ and a thermostat for controlling heat loss and water retention. Skin is a desirable model organ for testing cutting-edge regenerative medicine theories, with a focus on skin tissue regeneration for acute or chronic wounds. Stratum corneum (SC) and viable epidermis make up the epidermis, which refers to the skin's outer layer. The dermis, which is made up of fibroblasts and connective tissue, comes after the SC and is formed of living keratinocytes. The sweat glands, sebaceous glands, hair follicles, lymphatic vessels, blood vessels, and nerve fibres are housed in the dermis. The possible route for medication administration through the skin surface allows for both systemic and local drug delivery employing nanoparticles, which can quickly reach the opening follicles of the hair and skin diseases. Having access to living, immunologically active cells, nanoparticles that enter the epidermis have the potential to travel to the lymph nodes. The provision of a barrier of defense against microorganisms, UV rays, bacteria, and nanoparticles originating from the environment is one of the skin's most fundamental and crucial roles in mammals. The hair follicles in human skin barely cover 0.1% of the skin's surface; however, target medication delivery can be done via the follicular pathway to improve drug penetration. Skin has an acidic pH between 4.2 and 5.6. The skin's pH encourages the penetration of nanoparticles, and by using a solution with a lower pH, it is feasible to reduce the electrostatic force [1, 2].

Skin cancer illustrates one of the most prevalent types of carcinoma in humans, with one million new cases reported each year and it certainly poses a significant health burden in many countries [3]. According to estimations, each year 0.2 million instances of melanoma and 2-3 million instances of non-melanoma skin cancer occur in the world [4, 5]. Globally, there were 9.6 million mortality and 18.1 million new instances of skin cancer in 2018, according to estimates [6, 7]. By producing and activating a wide spectrum of chemicals in the skin, Ultra violet radiation act as a major contributor in skin carcinogenesis.

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Carcinogenic photons can cause direct or indirect DNA damage via reactive oxidative stresses (ROS) [3, 4].

Types of Skin Cancer:

Chronic skin exposure to UV radiation sources, both natural (from the sun) and artificial (from lights, etc.), is the main risk factor for developing cutaneous malignancies.

Skin cancer is mainly divided into two types; Melanoma skin cancer (MSC) and Non-melanoma skin cancer (NMSC).

1. Melanoma Skin Cancer (MSC):

Typical melanin-producing cells called melanocytes are the origin of melanoma, and their uncontrolled growth causes metastatic occurrences [8]. Melanocytes have the potential to manufacture melanin inside melanosomes through biochemical processes, which is ideal for skin pigmentation and protection against the harmful effects of UV radiation [9]. Multiple mutations may manifest in this diseased process, particularly in the epidermis at the basal layer. Melanoma can be divided into cutaneous and non-cutaneous variants depending on the region involved in its occurrence. MSC growth is influenced by a number of risk factors, but excessive ultraviolet (UV) light exposure is the predominant one. This exposure might cause melanocyte alterations that result in invasive and metastatic characteristics [2, 10].

Numerous studies have revealed that irregular sun exposure and ultraviolet (UV) radiations are key contributors to the growth of basal cell and squamous cell carcinoma, melanoma, and other types of skin cancer Reactive oxygen species (ROS) are produced as a result of UVA radiation, and these ROS ultimately lead to the oxidative degradation of proteins, lipids, and deoxyribonucleic acid (DNA) [4]. Even in the absence of mutations, the primary melanoma mutations (BRAF, MEK, NRAS, and MAPK) result in different melanogenic pathway functioning. However, a novel technique is desperately needed to provide therapeutic purposes in the management of melanoma due to the restraint approach associated to several medications [2, 11, 12].

Depending on the stage of the disease, different therapies are used for MSC. These include both traditional therapies like radiation (RT) and surgical excision as well as cutting-edge therapies including targeted therapy, immunotherapy, and combinations of systemic, topical, and transdermal medicines. MSC has a 90% cure rate when there is no metastatic ability, whereas patients with metastasis have a survival rate of only about 10% [13, 14, 15]. Lesions with well-defined borders should be surgically removed, although there are hazards involved, including lymph node involvement, metastasis, and relapse. Surgery, radiation therapy, immunotherapy, systematic therapy, and antibody therapy are only a few of the therapeutic options available for treating melanoma skin cancer. In addition to this, because of the targeted delivery of therapeutic moieties, nanotechnology-based techniques have become appealing tools in the treatment of melanoma [2, 9].

2. Non-Melanoma Skin Cancer (NMSC):

Non melanoma skin cancer is the most frequently occurring cancer type. The progression of non-melanoma skin cancer is depending on molecular pathways, which result in efficient therapeutic strategies for NMSC. Due to the reduced offensive action and invasive mechanism of NMSC, there is increased chance of survival and improved medical prospects [9, 16]. Squamous cell carcinoma (SCC) and Basal cell carcinoma are designated as keratinocyte carcinoma, because they are originate in keratinocytes [17]. BCC is prevalent in 70% of the population, while SCC accounts for 25% of cutaneous malignancies. Additionally, SCC is responsible for higher metastatic spread of the disease and death. BCC is associated with down regulation of hedgehog pathway, while SCC is the result of prominent upliftment of mutational and neoantigen events. NMSC is considered as a significant health burden due to their high incidence and they are more prevalent than all other types of cancer worldwide [17, 18, 19]. Beside genetics, multi-factorial elements contribute to the occurrence of neoplastic episodes in NMSC. The main factors are age, UV radiations, tobacco use, immunosuppression, genodermatoses, HPV infection, prescribed treatment, skin or bone infection, genetic disorder, inflammatory condition [16, 20, 21].

Surgery is a standard option for the treatment of NMSC, however, nonsurgical treatments are highly recommended depending on the extent and location of the lesions such as confocal microscopy, curettage, dermoscopy, cross-polarized light, electrodessication, topical drug delivery. Furthermore, raman spectroscopy and multiphoton microscopy are emerging as alternatives that act as a revolutionary tools for

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NMSC treatment [9, 22]. Various types of nanocarriers have been widely utilized as carriers for controlling the invasive pathways of NMSC [9, 17].

II. APPLICATION OF VARIOUS NANOCARRIERS IN SKIN CANCER.

Nanotechnology is an important tool for therapeutic agent delivery in cancer therapies. Nanomedicine improved the uptake of water insoluble compounds, provide prolonged release, improved bioavailability and permeation. Nanoparticles can combine with targeting ligands to reduce the off-target effect. This will increase the availability of drug in the targeting site as wll as reduce the adverse reaction associated with chemotherapeutic compounds [23].

1. Liposome

Liposomes are phospholipid vesicles (dimension of 50-100nm) having a bilayered membrane structure and an internal hydrophilic core. Liposomes are primarily composed of cholesterol and ecofriendly phospholipid. They can be multi-, oligo-, or unilamellar depending on the size and number of layers [23, 24]. Drugs pharmacokinetics, specificity and incidence of toxicity associated with anti-cancer therapies can all be improved using liposome. They have been dubbed as effective carriers of bioactive compounds into the skin because of the bilayers hydrophobic characteristics [9, 25]. The concept of employing liposomes treating skin conditions was initially put up in 1980 by Mezei and Gulasekharam. Numerous experiments have also been carried out to improve and develop liposome technology and combine it with other dermal delivery methods [17, 26, 27]. Liposomes have numerous properties including increased systemic circulation, penetrability, biocompatibility, diffusivity, rise in half-life, shielding effect, low immunogenic response and improved safety and efficacy. By placing numerous therapeutics on the surface of liposomes, researchers were able to achieve desired cytotoxic activity with a drop of undesirable effects due to target specific release [28, 29, 30]. Due to the lipoidal nature of liposomes, they can cling to the skin surface and fuse with SC lipids to release drugs into the tissue [17].

Deformable liposomes were used in a recent study performed by Marwah et al. for cellular dermal therapy. These liposomes were prepared by film hydration process with controlled release mechanism and incorporated with an antineoplastic agent, epigallocatechin gallatein (EGCG). In order to track changes in the liposomal characteristics, the formulation uses tween 20 at various concentrations. With a maximum dosage of surfactant, the entrapment of EGCG decreased. In addition, the deformability index decreased, which was confirmed by the values from 74 ± 8 to 37 ± 7, when the surfactant was present or absent respectively. This amplifies that the formulation may exhibit higher elastic behaviour. After a 2-h incubation period, the formulation demonstrated a significant cellular uptake with immortalized human keratinocytes (HaCat) and human dermal fibroblasts (HDFa) cells, which makes such controlled released liposomes a excellent candidate for reducing the effects of skin carcinoma [31].

2. Solid lipid nanoparticles

Solid lipid nanoparticles are spherical substances with diameters of 50-100 nm. High pressure homogenization method is used to prepare from a mixture of solid lipid that are both biocompatible and biodegradable, emulsifiers and water. Triglycerides, glycerides, fatty acid and waxes are the examples of lipids that are utilized. In early 90s, SLNs were developed to provide advantages relating to biocompatibility, long term stability and preventing drug degradation [32, 33]. The biopharmaceutics classification system (BCS) classes II and IV therapeutics are present in SLNs, which are colloidal candidates with a solid core made of rapidly liquefiable lipids and surrounding with an aqueous surfactant layer [9]. Additionally, they serve as carriers for both small and large sized therapeutics, genetic matter and vaccine antigens [34]. SLNs bind to the skin in the form of a monolayer to increase water retention within the skin and boost skin penetration [35]. Reduced toxic effects, larger surface area, prolong release profile, effective cellular absorption, improved solubility and bioavailability are some of the traits of SLN carriers. Inadequate drug loading, potential drug lose during storage are drawbacks associated with these carriers [36, 37]. The distinct feature of SLNs is their ability to increase the low risk ratio of topical therapeutic drug delivery through the epidermal layer. Additionally, the physiological lipid environment decreased harmful events and incorporated drugs burst releases can be prevent by the SLNs structure [38, 39].

In a different ground breaking study by Carbone et al. demonstrated the drug repurposing technique

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through the creation of SLNs that contained itraconazole as the target agent. The nanostructure used suppocire NB as the lipid matrix for topical delivery because of its stability and didodecyldimethylammonium bromide (DDAB) as the coating medium. The final formulation displayed different solubilities, which were apparent as clear suspension for suppocire NB and opaque cetyl palmitate (CP) and dynasan 114 (DYN) in the formulation. This discrepancy can be attributed to variations in the nanocarrier's particle diametric values. Due to the growth of protrusions that allow rapid release, the coated DDAB layer delivered a significant amount of drug to the malignant cells. The improved formulation demonstrated a potential synergistic cell viability reduction. This result can be attributed to the positive charge on the nanostructure surface, which allows a powerful binding between the particles and membranous site. The nanonecapsulated conjugate therefore exhibit a promising synergistic activity to produce therapeutic implications in melanoma [40].

3. Nanostructured Lipid Carrier

NLCs are the second generation of SLNs and made of solid lipid and embedded with liquid lipid. Either the lipid is contained by the solid matrix or it can be found on the surfactant layer [41]. They are showing a greater predilection for incorporating hydrophilic and hydrophobic therapeutics. They provide alluring advantages over SLN and liposomes including higher drug payload due to less leakage, better stability, simplicity of formulation due to their smaller particle size and the existence of disorder crystal structure [42]. Due to the unique characteristics of NLCs, numbers of recent studies have focused on their topical application. Additionally, NLCs can boost the probable solubility of encapsulated drug, creating a large concentration gradient on the skin that facilitates drug penetration [43]. The nanoscale particles of NLCs can securely cling to the skin surface and ensure controlled drug delivery [44]. Topical application of NLC gel creates a monolayered lipid film on the skin that act as a occlusive agent to improve skin moisture content and keep the skin hydrated by inhibiting trans-epidermal water loss (TEWL) [45, 46].

Using a pharmacological combination of quercetin (QT) and resveratrol (RES) in nanostructured lipid carriers, the dual nano system was investigated. Due to the remarkable solubility and stability profile attained, the nanonetwork was integrated into the lipid solvent, labrafil M2130CS. The increased impact could be attributed to limited crystallization, which eventually allowed for loading of significant amount of therapeutics into the lipid matrix. Zeta potential of the optimized formulation was around 10 mV, which indicates obstruction to coalescence development. Additionally, in contrast to the conventional formulation, the combinatorial alternative demonstrated an increased capacity of entrapment and loading mechanism, which led the researcher's to hypothesise that the nano-network crystal lattice may have been out of order. The amount of therapeutics that permeated into the skin was seen to have an increasing pattern, which may have been caused by the influence on lipid synthesis that hinders increased hydration. According to the researchers, the release of QT and RES through the NLC system was able to eliciting a remarkable cytotoxic reaction with lower inhibitory concentration than conventional gel. Additionally, compared to the normal gel, the drug disposition in the case of combination drug loaded NLC was three times greater, which is a considerable improvement in the delivery of pharmaceuticals into the epidermal and dermal layers [47].

4. Silver Nanoparticles

Silver nanoparticles exhibit distinct physical, chemical and biological characteristics due to their specific size, shape, shape, crystallinity and structural identity [48]. These have been detonated as spherical nanocarriers, nanorods, nanowires, nanocubes, and nanoplates [49]. AgNPs have attracted interest in pharmaceutical field because of their effective anti-oxidant, anti-inflammatory, anti-microbial and anti-carcinogenic mechanism. The anti-tumor effectiveness of silver nanoparticles is achieved by active and passive targeting due to their inherent cytotoxicity [50, 51]. AgNPs have the potential to be both anti-proliferative and anti-angiogenic. The DNA damage, genomic instability, chromosome breakage and disruption of in calcium homeostasis that eventually result in apoptosis and cytoskeletal instability are the signs of the anti-proliferative activity. This cytoskeletal disruption impairs cell division and cycle, which strengthens the anti-proliferative response to cancer cells [52].

5. Gold Nanoparticles

Gold nanoparticles (Au NPs) exhibit a range of coloured morphologies from 1 to 100nm. Due to their distinctive optical mechanism, unique

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properties, improved stability, and ease of fabrication, Au NPs have become more significant in the biopharmaceutical field [53, 54]. The nanoparticles serve as powerful chemical sensors, drug delivery vehicles, and agents for bio-imaging with extensive applications in cancer therapy [55, 56]. They are widely recognised as distinctive conjugation candidates for a wide range of pharmacological moieties due to their high surface to volume value, non-immunogenicity, safety, and numerous functional agents [57]. Without a doubt, gold nanoparticles can be used as effective tools for achieving desired anti-carcinogenic response for skin cancer occurrences. [58, 59].

In a study, a combined therapy for skin tumours was suggested that involved loading curcumin into liposomal nanocarriers that were encircled by gold nanoparticles and operated by a light-sensitive mechanism. When exposed to laser treatment, the release rate of gold nanoparticles incorporated with CUR-liposomal moieties was significantly higher than that of the plain CUR-liposome complex, which may be due to the instability of the liposomal nanocarriers' outer membranes under the influence of intense heat waves. Results showing that both complexes displayed an effective endocytosis pattern in comparison to free CUR further demonstrate that the presence of gold on the surface of liposomal nanocarriers has no impact on endocytosis. The results demonstrated that using such in-situ phenomena is a successful method for using gold-liposomes made of hydrogenated soy phosphatidyl choline (HSPC) to combat skin malignant cells [60].

6. Ethosomes

These elastomeric vesicles are made up of ethanol, water, and phospholipids with small amounts of cholesterol and other lipids [61]. The elasticity of ethosomes, first described by Touitou et al. in 1996, results principally from the interaction between cholesterol and ethanol on the temperature at which phosphatidylcholine transitions into its phase transition state [62]. Due to their structural shape and abundance of lipid bilayers, ethosomes serve as entrapment carriers for hydrophilic, lipophilic, and large molecular weight compounds [63, 64]. Increased ethanol production results in negatively charged medications that are more stable, penetrable, and bioavailable. Drugs are delivered via ethosomes into the dermal layer for systemic circulation [65]. Ethosomes of econazole nitrate were more stable and produced higher antifungal efficacy with controlled release when compared to liposomal and hydro-ethanolic gel-based formulations [66]. In a different study, Fang et al. showed that during photodynamic treatment (PDT), 5-aminolevulinic acid (ALA) enclosed in ethosomes penetrated the skin more quickly than its liposomal formulation [67].

7. Niosomes

Niosomes are non-ionic liposomes that can be hydrated with or without cholesterol. They are constructed of non-ionic surfactants. Niosomes are far more stable, less expensive, and more practical to produce than traditional liposomes [68]. By combining with the lipids, niosomes are able to change the SC barrier. By replacing lost lipids and minimising trans epidermal water loss, the particles can further improve the smoothness of the SC [69]. Additionally, they are influenced by the physicochemical characteristics of the medication, the vesicle, and the lipids utilised in the niosome manufacturing process. Numerous studies have been done on the role that charge, cholesterol, and surfactants like Span 40 and Span 60 play in promoting the skin's ability to absorb and retain niosomes [68, 70].

8. Transethosomes

Transethosomes are lipid vesicles that include characteristics of both transfersomes and ethosomes and were first described by Song CK et al. [71]. These contain phospholipids and membrane softening edge activators like tween 80, span 80, and sodium cholate. They are made up of an internal aqueous environment and are surrounded by a lipid bilayer structure. Hydrogenated soya phophatidylcholine and phophatidylcholine are utilised as phospholipids [72, 73]. Their synthesis is carried out via the rotary evaporation-sonication method, commonly known as the thin film hydration approach. The drug contained in transferosomes can be effectively retained in the skin and easily prevented from occurring in cutaneous blood [74, 75]. These clever transdermal drugs have produced remarkable results and are also linked to have self-regulating and self-optimizing characteristics [76, 77]. Transferosome-loaded preparations serve as transdermal immunisation agents, peripheral drug targeting mediators, and effective tools for the transdermal administration of a variety of therpaeutic molecules [78].

Jangdey et al created transferosomes that contained apigenin as the anti-cancer agent to achieve

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optimum skin penetration. Entrapment efficiency (EE) initially increased after a lower amount of surfactant was added to the nanoformulation, but as the concentration of surfactant increased, the EE value decreased. The dwindling effect observed suggest the formation of pores in the bilayered structure. The observed diminishing effect suggests that pores have formed in the bilayered structure. As a result of the surfactant-drug bonding, the optimised nanoformulation may have displayed an elevated EE as compared to apigenin solution. The burst-to-sustained transition in the release profile was caused by the presence of free drug in the superfacial layer, while the sustained transition may have been caused by the presence of apigenin in the inner lipidic environment. The nanocomplex demonstrated a significant penetration response, which is explicable due to the presence of surfactants and the lower particle size. Overall, the generated nanocandidates demonstrated expected anti-tumor activity and can be considered effective anti-cancerous agents for skin cancer. [79].

9. Nanofibers

Nanofibers (NFs) are fascinating solid fibres with submicrometric diameter values that have a high porosity and a huge surface area [80]. These nanocarriers are made using a variety of techniques, including template synthesis, drawing [81, 82], the phase separation technique, electrospinning [83], and the self-assembling approach [84]. Electrospinning is the most widely used of these due to its affordability and ability to produce large numbers of nanofibers with hetergogenous moieties [85, 86]. By carefully integrating the appropriate technology, polymer solution, and environmental factors, nanofibers can be readily modified based on their diameter, porosity, and mat thickness. [87, 88]. Nanofibers are attractive prospects for biomedical applications because to their high surface-to-volume ratio, enormous porosity of the nanofiber mesh, decreased obstruction to mass transfer, flexible handling, variable morphological characteristics, and increased mechanical force [89, 90]. Previous research has shown that NFs have the ability to act as scaffolds with the potential to encapsulate anti-carcinogenic medicines as well as controlled release capabilities for diagnostic applications, including drug administration and cancer therapy [90, 92].

In a recently published study, gold nanoparticles (Au NPs) and curcumin (CUR) were added on a platform made of nanofibers as a non-toxic and environmentally friendly method. The nuclear membrane and DNA of the cells treated with the control agent did not significantly change, whereas the cells treated with nanofibrous were distinguished by an induced apoptotic response. The treatment of poly vinyl alcohol (PVA) loaded gold nanoparticles and poly capro lactone (PCL) linked curcumin resulted in a significant decline in the viability of A431 cells, further validating the potential of AuNPs and curcumin to work together to limit the proliferation of malignant cells. 3 T3 fibrioblastic cells demonstrated a remarkable cytotoxic mechanism, as shown by the effective cell viability. As a result, Au-CUR nanofibers are revealed to be an effective vehicle for anti-cancerous capabilities against skin cancer [93].

10. Dendrimers

The term "dendrimer" refers to hyper-branched, clearly defined, 3D polymeric nanostructures that exhibit homogeneous shape and size, biocompatibility, polyvalency, and precise molecular weight [94-97]. The phrase "dendron-meros" (tree-like) and "meros" (part of) are two Greek words that were used to describe these macromolecules when they were first discovered by Tomalia in 1985 [98, 99]. Divergent and convergent methods are used to synthesise dendrimers, respectively [100]. Three topological elements make up a typical architecture: a central core, construction blocks with repeating branching units, and various functional moieties dispersed across the periphery [101, 102]. Dendrimers are identified as monomolecular micelles by the internal hydrophilic and hydrophobic pockets, creating room for external therapeutic substances [103-106]. Due to their numerous roles as catalysts, gene transporters, drug carriers, biosensors, solubility modifiers, diagnostic candidates, and biological indicators, they hold a variety of significance. For intracellular drug administration and to increase the bioavailability of the molecular agents, dendrimetric complexes of anti-tumor therapeutics have shown the ability to overcome efflux transporter [107-109].

A combined approach of chemotherapy and immunotherapy was used by Xia et al. to examine the anti-metastatic potential of doxorubicin via G4 PAMAM dendrimer, cytosine - phosphate - guanine based oligonucleotides were added and then this conjugate was coated with low molecular weight heparin. Due to the synergistic effects of doxorubicin and heparin, the formulation's ability to invade was demonstrated by a decrease in

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B16F10 cells, with an invasion rate of about 29.22%. Anti-metastatic properties of heparin were demonstrated by the additional obstruction of mesenchymal-based malignant cell transformation in addition to the degradation of the actin cytoskeleton. The combined effectiveness of doxorubicin and cytosine-phosphate-guanine oligonucleotides (CpG) oligonucleotides is responsible for the in-vivo results, which showed a remarkable inhibition of tumour growth and volume. Thus, the multifunction platforms were effective in managing melanoma tumours [110].

III. CONCLUSION

The novel approach of nanotechnology to addressing a variety of skin problems has revolutionised the area of medicine. With benefits such as tumor-specific medication administration, improved therapeutic efficacy, decreased incidence of adverse events, and improved tumour invasional dissemination, emerging nanotechnological techniques play a crucial part in illustrating potent anti-carcinogenic mechanisms. When appropriate chemotherapeutic medications are loaded onto properly chosen nanocarriers, the outcomes in terms of dosage reduction when compared to traditional therapies have been encouraging, easing the burden on the medical community and improving patient health.

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