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Apitherapy and Nano chemotherapy of skin cancer treatment reviews

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Abbreviation

LARC	Agency for Research on Cancer

Chapter 1

1. Introduction

1.1. Generally cancer

Over eight million people die from cancer each year, making it a serious worldwide health concern. 7.6 million deaths globally are attributed to cancer, according to a recent estimate from the International Agency for Research on Cancer (LARC). Similarly, an estimated 12.7 million new cases occur year. It has been stated that developing nations had a higher risk of cancer; a survey found that only emerging nations accounted for 63% of cancer-related deaths (Ewing B, Camen P. 2000). Cancer is a complicated condition with multiple underlying causes that arises from the interplay of the host and environment. Cancer is characterized by a number of characteristics, such as resistance to growth signals, insensitivity to signals that stop cell division, unchecked replication, apoptosis evasion, persistent angiogenesis, and, ultimately, metastasis—the ability to spread to other organs. 2 (Wright FA, Lemon WJ,

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Zhao WD, Sears R, Zhuo D, Wang JP, et al, 2001) The extracellular environment and deregulation of several regulatory proteins are evident in the microenvironment of benign tumors, and these factors are crucial for the initiation and progression of malignancies. 3 (Pavlova NN, Thompson CB , 2006) Prior to 1950, the only recommended course of treatment for cancer was surgery. Radiation therapy was used after 1960 in order to manage localized disease. As time went on, it became clear that using radiation and surgery alone to treat cancer is ineffective compared to using them in combination. Treatment options available today include immunological-mediated therapy, biological substances, and pharmaceuticals. As of right now, we haven't developed a treatment that defies death and shortens the length of time patients with metastatic cancer survive. Drugs that target tumors have the potential to revolutionize the treatment of neoplastic cancer by identifying the pathways and properties of various tumor entities. The foundation of radiation treatment is the employment of physical particles, such as protons, electrons, and different ions, to destroy malignant cells. High energy radiations damage genetic material in cells, stopping cell division and preventing them from proliferating. This is how radiation treatment works. Radiation therapy is administered with the goal of shrinking the tumor if it is done prior to surgery. When radiation therapy is used following surgery, it destroys tumor cells that remain and lowers the risk of cancer relapsing. 4 (Delaney Get al. ,2005) Chemotherapy is used either alone or in conjunction with radiation therapy to treat systemic malignancies since radiation therapy acts locally. For the majority of cancer types, chemotherapy is seen to be the most often utilized and effective treatment. Chemotherapy medications specifically target tumor cells, primarily producing reactive oxygen species that genotoxically kill tumor cells. 5 (DeVita VT, Chu E, 2008) Chemotherapy, however, also damages healthy cells, which can result in a variety of dose-dependent side effects include exhaustion, nausea, hair loss, vomiting, and in severe situations, death. 6 (Aslam MS et al , 2014) Dendritic

cell-based immunotherapy is considered the most effective advanced cancer treatment modality since it manipulates the immune system to eliminate tumors without causing any side effects. 7 (Jiang Wet al , 2012)

Understanding of the cancer

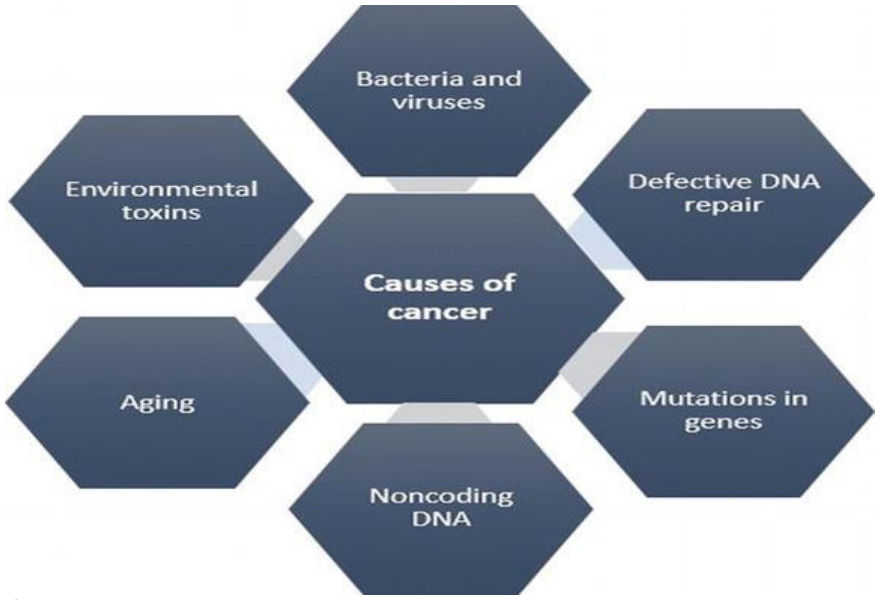
Cancer is an aberrant state in which a population of cells grows uncontrollably by disobeying the physiological guidelines for cell division. Because they have some degree of self-sufficiency, cancerous cells do not react to the signals that initiate the regular cell cycle, which causes the altered cells to grow and proliferate uncontrollably. 11 (Hanahan D, Weinberg RA, 2000) It may be lethal if the malignant cells continue to proliferate. In actuality, metastasis—the term for the spread of cancer cells to other tissues—is the cause of 90% of cancer-related fatalities. Normal cells grow in an interdependent manner during mitosis and depend on the availability of outside growth stimuli. Therefore, cells stop reproducing when their supply of these growth signals is reduced or stops altogether. Lumor cells, on the other hand, develop in spite of all stimuli or signals. 12 (Lum 1] et al, 2005) Additionally, normal cells have the capacity to prevent interaction. They stop dividing when there are sufficient neighboring cells, or when a certain threshold is reached. On the other hand, cancer cells are unable to inhibit interaction, which causes an undesired cell mass to form. 13 (Hahn WC et al , 1999)

reasons why cancer occurs

Cancer develops and spreads due to a variety of internal variables (hormones, immune systems, and mutations) as well as external environmental influences (smoking, toxins, infectious organisms, and radiations). Together, these components result in aberrant cell behavior and unchecked growth. The resulting atypical cell mass in the body expands and influences surrounding normal tissues; occasionally, it also spreads to other parts of the body (metastasis). 17 (Ames BN, Gold LS, Willet WC, 1995)

Chemotherapy

Chemotherapy stops the growth of tumors by destroying their ability to divide and inducing apoptosis. The body's natural biological processes remove damaged or surplus cells from the body, allowing new cells to proliferate. In contrast, because they are not subject to apoptosis, tumor cells have a higher potential for division and an immortal nature. Thus, in malignant bulk, the ratio of cell growth to cell death is high, in contrast to normal bodies where cell



proliferation is balanced and regulated by cell death. Here, chemotherapy works to alter the tumor cells such that they either cease to develop or die; hence, the two categories of chemotherapeutic medications are, respectively, cytotoxic and cytostatic (biological medicines). (5) (DeVita VT, Chu E, 2008) Chemotherapeutic medications, however, also attack normal cells, which, depending on the dosage, may cause a range of adverse effects, including fatigue, hair loss, nausea, vomiting, and so on. Patients who get intense chemotherapy suffer from immunocompromised states, which can lead to fatal infections and other complications. Only 132 of the chemotherapeutic medications that have been found have FDA approval. These medications are

Comment [m2]: Define

made with the specific intention of killing tumor cells by producing reactive oxygen species, or a genotoxic impact. However, these medications also have some effect on the body's natural cells . 37 (Rodgers GM et al, 2012) At the beginning of the 20th century, chemotherapy became a common cancer treatment. A nationwide initiative to create pharmaceuticals was launched in 1955 under the name Cancer Chemotherapy National Service Center, thanks to the effects of medications examined in four programs carried out during World War II. The 1960s and 1970s saw the cure of acute pediatric leukemia and advanced Hodgkin's disease with combination chemotherapy, which contributed to the general acceptance of medications' potential to treat complex tumors. Additionally, this promoted research on adjuvant chemotherapy with support from the National Cancer Program. These days, testing the efficacy of novel medications and developing tailored treatments involves a significant screening procedure based on molecular investigations of anomalies in cancer cells. Chemotherapy has advanced thanks to this. 5 (DeVita VT, Chu E, 2008) (Abbas and Rehman, 2018)

A- Direct action → radiation → DNA damage → Cell death

B- In-direct action → radiation → Free radiation → DNA damage → Cell death

Types of cancer

i. skin cancer
ii. breast cancer
iii. gastric cancer
iv. prostate cancer
v. liver cancer
vi. bladder cancer
vii. lung cancer …Etc

Skin cancer

The majority of the time, skin exposed to the sun develops abnormal skin cell growth, which is known as skin cancer. However, this prevalent type of cancer can also develop on skin parts that aren't often exposed to sunlight. Melanoma, squamous cell carcinoma, and basal cell carcinoma are the three main forms of skin cancer. And have 4 types melanoma, squamous cell carcinoma, non-melanoma , basal cell carcinoma also range of UV is three types UVA (400–320 nm) only UVA is caused to skin cancer , UVB (320–290 nm), and UVC (290–200 nm), according to wavelength. UV light can penetrate the skin deeper the higher its wavelength. Nonetheless, each UV component's wavelength has an inverse relationship with the energy it contains. As a result, UVA has the least energy but can penetrate the skin deeply. Although there is strong evidence that UVA can potentially cause skin damage in humans in this figure show how can

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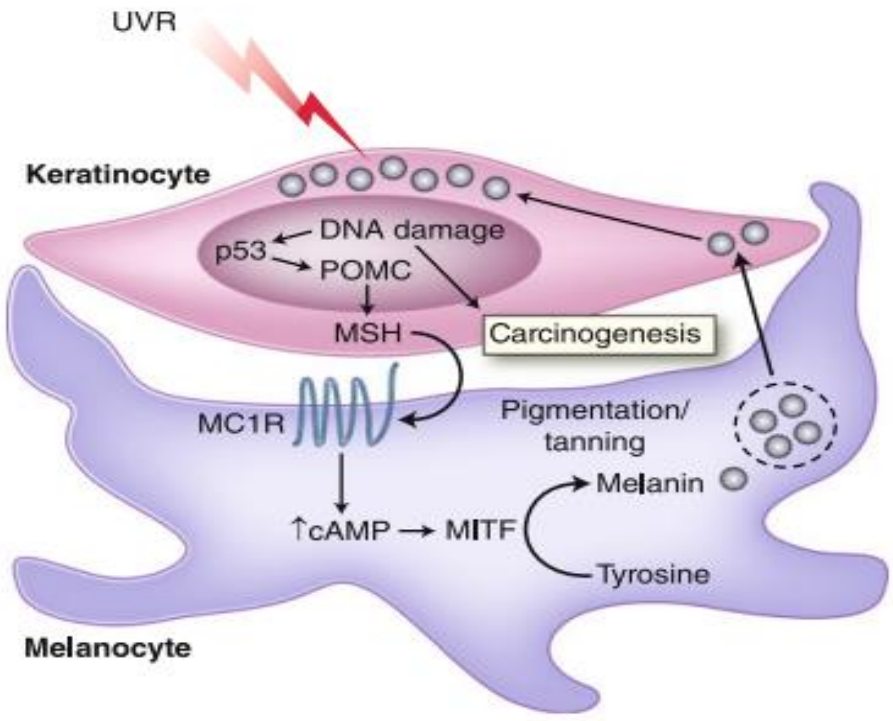

Figure 11. skin melanocyte cancer

UV is caused to cancer skin (Garibyan and Fisher, 2010)

figure-1- *(Diagram illustrating the molecular processes involved in the carcinogenesis pathway generated by UVR and tanning. UVR damages keratinocyte DNA, which results in tanning and the development of skin cancer. The pro-opiomelanocortin (POMC) gene is expressed when DNA damage activates the p53 gene. Melanocytestimulating hormone is produced by translationally cleaving the POMC gene product (MSH). MSH binds to the melanocortin-1 receptor (MC1R) on melanocytes and causes an increase in cAMP levels. Melanocytes release MSH. Tyrosine is then converted to melanin by increasing the transcription of the microphthalmia-associated transcription factor (MITF) Melanin is transferred to keratinocytes via melanosomes, where it functions to shield the nucleus from more UV radiation. The look of tanning is also caused by the buildup of melanin in keratinocytes)*

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In the US, skin cancer is the most prevalent type of cancer. Most malignancies of the skin are not melanomatous. Skin tumors that are not malignant melanoma are derived from keratinized epithelial cells. Squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) are two of these malignancies. Though it makes up only 2% of malignant skin cancers, melanoma is the most common cause of mortality from the disease. In the US, skin cancer was identified in over 2 million cases in 2010. The most prevalent type, BCC, typically grows slowly and is invasive only in certain areas. SCC makes about 20% to 30% of instances of nonmelanomatous skin cancer, making it the second most frequent type.

Prolonged exposure to UV radiation is the primary risk factor. When elderly fair-skinned persons exhibit scaly, indurated lesions on sunexposed areas, mainly on the head and neck, a diagnosis is typically suspected. With a dermatoscope, proper lighting, and magnification, clinical diagnosis accuracy can be improved. For a conclusive diagnosis, a biopsy along with histopathologic confirmation is needed. Since the depth of the lesion determines

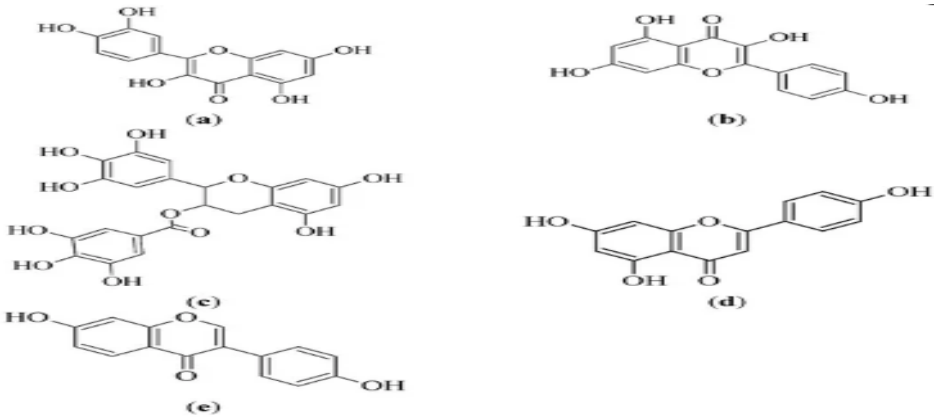
the course of treatment and prognosis, a full-thickness biopsy is necessary for the examination of melanoma. Worldwide, the number of cases of all types of skin cancer has been rising. Research has indicated a rise in the occurrence of melanoma in younger people epidemiologic studies have revealed as high as a 50% prevalence in those between the ages of 35 and 65. (American Cancer Society Cancer facts, 2010)

Without of UV there are other risk factors for skin cancer, such as smoking, exposure to specific chemicals, higher UV radiation exposure at work and during leisure, and elderly populations have many way to improve cancer like Radiation, chemotherapy, and surgery are the three primary cancer treatments. However, systemic side effects, severe toxicity, and drug resistance in chemotherapy remain the biggest challenges to cancer treatment (6.7.8) (Enrica Caló, 2015 Vitaliy V. Khutoryanskiy . Sérgio Roberto Montoro ,2014. Sandhra M. Carvalho2018 …etc)

However hydrogels is treatment of skin cancer Hydrogels have been regarded as standard and perfect local therapeutic platforms. The three-dimensional (3D) lattice of hydrogels, which are hydrophilic polymers, allows for the retention of a significant amount of water. Different types of biocompatible synthetic or natural polymers can be used to prepare them. Physical gels are the term for hydrogels. But in chemical gels, cross-linking in a solution or dry state creates the network of covalent bonds. Chemical hydrogels are often offered in two different ways. first hydrogel synthesis with polymerazation Hydrogels are created in a second step by crosslinking ready-made, water-soluble polymers. (L. Heller , 2021) (12) (Marzi et al., 2022)

described Surgery alone is not a suitable treatment for advanced metastatic melanoma. As a result, further therapeutic approaches are needed, including immunotherapy, bio-chemotherapy, chemotherapy, and adoptive cell therapy like Polymeric-based drug The most intriguing medication delivery methods for

treating cancer are those based on polymers. Using polymers as carriers for antineoplastic medicines has a number of benefits, including as improved bioavailability, controlled drug release, selective organ or tissue distribution,



higher solubility of the medication, and a decrease in the overall dose needed. Furthermore, the negative side effects of hazardous anticancer medications can be greatly reduced by the combination of polymers with them.

In general, phytochemicals with anti-inflammatory, immuno-modulatory, and antioxidant qualities have the greatest potential to act as chemopreventive agents against skin malignancies.(Katiyar, S.K. 2011)(37) Several efforts have been undertaken to determine the relationship between phytochemicals' antioxidant qualities and their potential to prevent cancer. The anti-oxidant activity of a phytochemical is thought to be a sign of possible anti-cancer action, even if no hard proof of this connection has yet been discovered. Terpenoids, flavonoids, and carotenoids are a few phytochemical groupings with strong anti-cancer potential, Terpenoids, flavonoids, and carotenoids are a few phytochemical groupings with strong anti-cancer potential. 1st (flavonoids) Two benzene rings joined by a linear carbon chain and an aromatic chromophore define the chemical structures of flavonoids, which are acetogenins found in plant and floral pigments. The aromatic chromophore is responsible for the vivid hues of plant parts high in flavonoids. Flavonols, flavanones, flavones,

isoflavones, flavan-3-ols (catechins), and anthocyanins are the primary classes of flavonoids. The chemical structures of a few flavonoids that have been shown to have anti-cancer properties are shown in Figure 2 and will be covered in the following sections. (44) (Corcoran, M.P., 2012)

Comment [m5]: Where are???

Chemical structure of derivate flavonoids

(a) quercetin (b) kaempferol (c) EGCG (d) apigenin (e) daidzein

Depending on other physiological variables, the anti-oxidant effect of flavonoids may either stimulate or inhibit the growth of tumors. Therefore, not all flavonoids would be helpful in chemotherapy or chemoprevention for cancer. (Chinembiri et al., 2014)

Malignant melanoma The most deadly type of skin cancer is called cutaneous malignant melanoma, or CM. The malignancy known as CM, which is thought to originate from epidermal melanocytes, is frequently resistant to treatment and prone to metastasis. Its frequency has increased steadily and considerably over the past few decades.(1,12)(D'Orazio J,2013 Narayanan DL,2010) Women's lower legs have been reported to have melanoma, yet it can also occur on the head, neck, or other parts of the body. The only "cure" for melanomas that are discovered early on is surgical removal. Despite this, CM have a low long-term survival rate for advanced disease because of how quickly they invade and spread Although targeted therapy and immunotherapy have made advancements in the treatment of cancer, CM remains particularly difficult to treat once it has progressed beyond its primary site. Compared to NMSC, the epidemiology of CM is better documented. Melanoma is thought to have contributed to 37,000 fatalities in Europe in 2000 Furthermore, 132 thousand new instances of melanoma are thought to emerge annually worldwide. Caucasians have incidence rates that are at least 16 times higher than those of African Americans and 10 times higher than those of Hispanics. Additionally, according to estimates from the World Health Organization (WHO), up to 60,000 persons

globally pass away from malignant skin cancer each year, with about 40,000 of those deaths being reported. Although making up fewer than 5% of all skin cancer cases in the United States, CM is the primary cause of skin cancer-related mortality.

Non-melanomatous The incidence of NMSC is far higher than that of melanomas; however, luckily, the majority have far better long-term prognoses and are considerably easier to treat. BCC and SCC, the two main types, are both produced from keratinocytes found on the epidermis. Their management is significantly simpler because they tend to stay localized to their primary site of disease, which makes them less lethal than melanoma. Most keratinocyte cancers, which are catastrophic, develop on the face and arms, the parts of skin that are most exposed to ultraviolet light. Furthermore, these NMSCs can cause severe deformity and are the most prevalent type of cancer in people.(Narayanan DL…etc , 2010)(12) (Simões et al., 2015)

BASAL CELL CARCINOMA (BCC):

This type of skin cancer starts in the epidermis's basal layer and its appendages. It can appear anywhere on the body, but it more frequently appears on sun-exposed parts including the nose, ears, cheeks, and backs of hands since it is brought on by UV radiation-induced cell abnormalities. It is a malignancy with a sluggish growth rate that rarely spreads.

The American Cancer Society estimates that in 2006, about 3.5 million nonmelanoma skin cancer cases were treated in the US. It is estimated that BCC accounted for 80% or more of these skin cancer cases. White people are more likely to get this cancer, and men are 30% more likely than women to get it. 30% of people will acquire BCC in their lives. BCC is more common as people age and become closer to the equator. Within five years after receiving a diagnosis of BCC, almost 40% of patients get another lesion. (Karagas MR, Stukel TA, Greenberg ER, et al. , 1992)

Risk Factors

Ionizing radiation

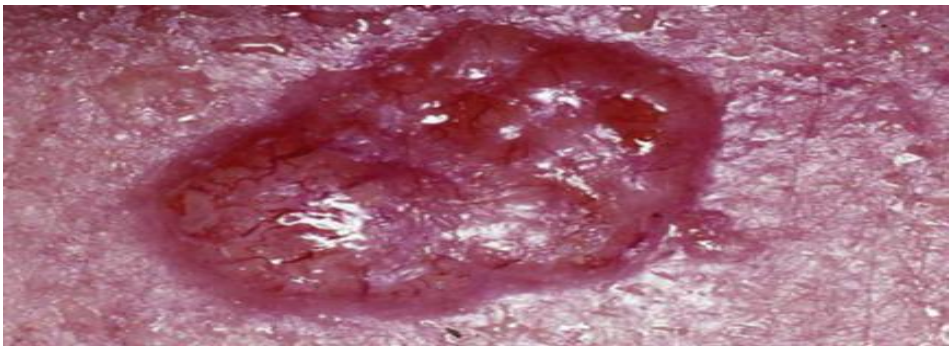
Chronic arsenic exposure

Gorlin syndrome, also known as basal cell nevus syndrome, is caused by an autosomal dominant mutation in the human patched gene.

Basal Cell Carcinoma

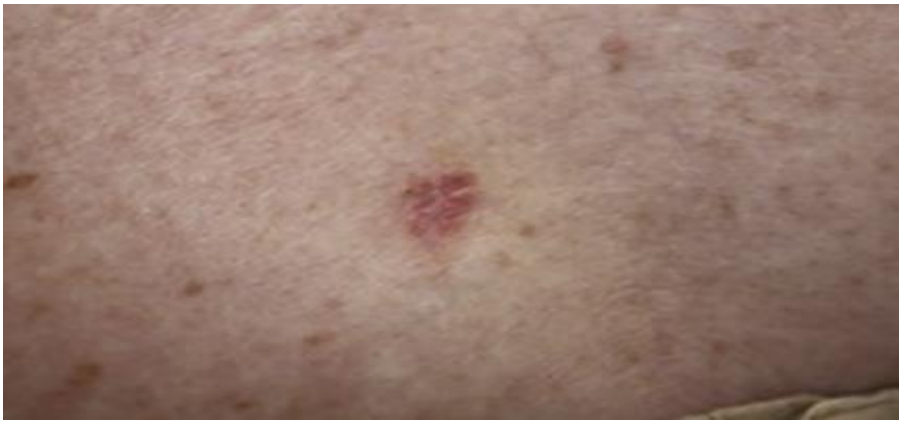
Nodular Basal Cell Carcinoma

The most typical facial manifestation of nodular BCC is a white, skin-colored, or pink papule. The papule may have ulceration, telangiectasias, and a translucent, pearly appearance.



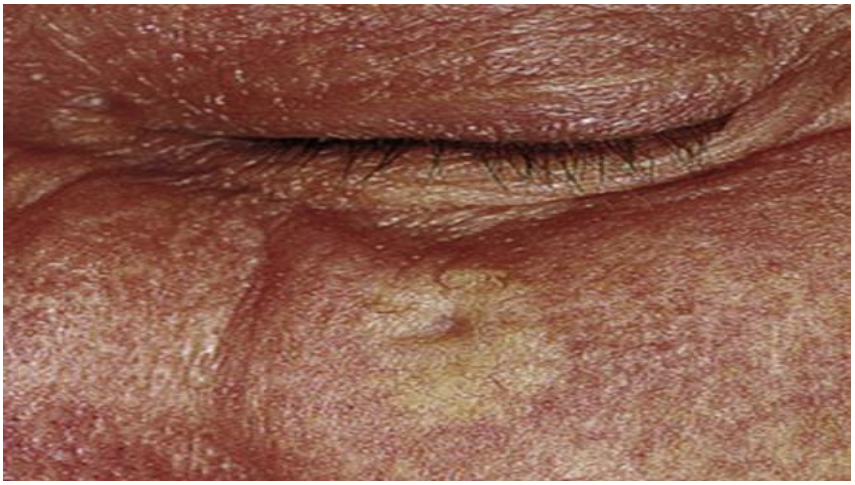
Superficial Basal Cell Carcinoma

Typically, superficial BCC manifests as an erythematous, scaly papule or plaque on the trunk. Transparent papules may line the lesion's edge, and atrophic tissue may be visible in the lesion's center.



Morpheaform Basal Cell Carcinoma

A skin-colored or erythematous papule or plaque is the typical presentation of morpheaform BCC. The lesion may have uneven boundaries, induration, and atrophy, giving it a scar-like appearance. (Linares et al., 2015)



New technological perspectives for skin cancer treatment

i. Nanocarriers : In recent years, there has been a growing interest in colloidal carriers. Nanoparticles, nanoemulsions, nanosuspensions, liposomes, micelles, vesicles, and soluble polymer–drug conjugates are some examples of investigational methodologies. Given the variety of colloidal carrier systems available, it is unclear which one would be best suited for the intended use.

   A. Liposomes
   B. Nanosuspensions and nanoemulsions
   C. Lipid nanoparticles
   D. Carbon-based nanoparticles …Etc

Treatment by Nano-Particles **NP :**

Over the past ten years, there has been a noticeable increase in the usage of nanoparticles (NPs) as a therapeutic delivery system, especially for applications aimed at the skin. Because the skin acts as a physical and immunologic barrier, it must be delivered to with careful thought. Certain technologies need to take into account not just the target but also the delivery method. A broad range of NP-based solutions have been developed in response to this particular difficulty, with the aim of accurately addressing these factors. This review article summarizes the types of NPs, discusses the current state of NPs for skin cancer prevention and therapy, and describes the use of NP-based technologies for medication delivery targeting the skin.

Because the skin constitutes an immunologic and physical barrier, it is important to take specific caution when targeting this region for NP drug delivery. This

location is rich in immunological populations, including innate lymphoid cells, skin-resident and skin-homing effector and regulatory T cells, dermal dendritic cells, and epidermal Langerhans' cells (Soulika, 2019). The stratum corneum, which is made up of a thick matrix of dead, dehydrated keratinocytes inside of an organized lipid layer, acts as an initial barrier to prevent NPs intended for the skin from entering the skin. NPs can be created to work in harmony with the surrounding environment, depending on the mode of administration and desired level of targeting, i.e., topical application with transdermal delivery or direct injection to the location.

Excipient agents, such as fatty acids, esters, alcohols, amines, and lipids that physiochemically alter the skin barrier, can facilitate penetrance and delivery of typical drug formulations into and through the stratum corneum, epidermis, and dermis (and thus availability for systemic absorption).

The skin has evolved to be highly protective against the majority of naturally occurring environmental NPs (such as bacteria, dust, virus particles, or allergens), which do not readily penetrate the skin unless the skin barrier is disrupted by disease or specific interventions. This presents a number of challenges for NP-facilitated drug delivery to the skin.

Most naturally occurring environmental NPs (such bacteria, dust, virus particles, or allergies) are highly resistant to the skin's inherent defenses against them; only when the skin barrier is compromised by illness or particular treatments can these NPs easily pass through the skin.(Chang et al., 2023)

Bee product to treatment of cancer cell

Honey has long been recognized for its therapeutic and health-promoting qualities. Honey is a compound made by different kinds of honey bees (Apis sp.) from plant blossom nectar, plant phloem feeding insect exudates (honeydew), or a combination of the two. 10 (E Pichichero, L Canuti, A Canini , 2009)

While honey primarily consists of a concentrated aqueous solution of inverted sugars (fructose and glucose), it also includes additional sugars, organic acids, amino acids, vitamins, minerals, antioxidants, and other substances. Carotenoids, flavonoids, and phenolic acids [11-13]. (AM Aljadi, MY Kamaruddin, 2004, M Al-Mamary, A Al-Meeri, M Al-Habori 2002, N Gheldof, XH Wang, NJ Engeseth ,2002)

The phenolic and flavonoid content of the different types of phytochemicals found in honey is relatively high. These phytochemicals include simple and polyphenols like acacetin, apigenin, caffeic acid, caffeic acid phenethyl ester (CAPE), chrysin, galangin, kaemfereol, pinocembrin, pinobanksin, and quercetin for example. 14 (S Sabatier, MJ Amiot, M Tacchin, S Aubert, 1992) Generally speaking, flavanoids have anticancer effects. [17] (CO Middleton, EJ Harbored , 1986)

Apart from its antioxidant characteristics, honey is believed to possess a wide

range of medicinal capabilities, such as antibacterial activity. 19-23 24-25 (A Tonks, RA Cooper, AJ Price, PC Molan, KP Jones , 2001 , JH Dustmann, 1979,K Brudzynski,2006A Jeddar, A Khassany, VG Ramsaroop, A Bhamjei, IE Haffejee, A Moosa 1985)

What's interesting about this, though, is that honey—especially jungle honey, which is wild honey harvested from forested areas—can serve as a foundation for the creation of innovative treatments for individuals suffering from soft and hard (tumor) tissue cancers. Apart from impacting the chemotactic activation of reactive oxygen species and neutrophils 26 (M Fukuda, K Kobayashi, Y Hirono, M Miyagawa, T Ishida, EC Ejiogu, *et al.* 2011)

It has been demonstrated that jungle honey significantly inhibits human breast, cervical, oral, and osteosarcoma cancer-derived cell lines in vitro. [27,28 (Fauzi AN, Norazmi MN, Yaacob NS ,2011 , Ghashm AA, Othman NH, Khattak MN, Ismail NM, Saini RN. 2010)

and enhanced the effects of conventional chemotherapy with cyclophosphamide or 5-flourouracil 32 (Wattenberg LW.1992)

Prostate cancer has been treated with a few of the main phytochemicals found in honey, including lycopene, genistein, resveratrol, and epicatechin-gallate.33 34 Heuson JC, Legros N, Heimann R. 1972, Moutsatsou P. 2007)

Anticancer activity of propolis

Honey bees make propolis, often known as bee glue or putty, from the resin that they gather from foliage. 43 (Pietta PG, Gardana C, Pietta AM. 2002) This is mixed with pollen, beeswax, and salivary gland secretions—which are high in enzymes. Depending on the plants from which the resinous material was harvested, the color can range from yellow to black. This color will also rely on the local flora, 44 Propolis has been the subject of recent research about its possible anticancer properties. 20 21 22 (Jaganathan SK, Mandal M , 2010 , Pichichero E, Cicconi R, Mattei M, Muzi MG, Canini A. 2010 Samarghandian S, Afshari JT, Davoodi S 2010) It has been observed that artepillin C, which is extracted from propolis, causes mass necrosis, abortive mitosis, and apoptosis in carcinoma and malignant melanoma cells to cause cytotoxicity. The inhibition of tumor growth was probably brought about by both increased immunity and direct cytotoxicity of the tumor. 51 (Kimoto T, Arai S, Kohguchi M, Aga M, Nomura Y, Micallef MJ, et al. 1998) (Premratanachai and Chanchao, 2014) Currently, in the market, there are different types of propolis based on their origin. The popular propolis types are Brazilian, Taiwanese, Chinese, Okinawa, Indian, Turkish, Polish, Greece, Cuban, and African. They also differ from one another in a color (red/brown/yellow/green) and texture, depending on the origin of place (geographical) as well as climate [5,6]. (Pobiega K, Gniewosz M, Kraśniewska K, 2017. Bankova V. 2005) Resin (40–50%), wax (25–30%), essential oils/fatty acids (8%–10%), bee pollen (3%–5%), organic acids and amino acids (1%–3%), vitamins, and minerals (1%–3%) are the main ingredients of propolis. 8 10 9 (Anjum SI, Ullah A, Khan KA, Attaullah M, Khan H, Ali H, et al,2019. Bueno-Silva B, Marsola A, Ikegaki M, Alencar SM, Rosalen PL.2017 , Patel S. 2015) More than 300 distinct types of constituents, including polyphenols (flavonoids, flavones, flavonols, and phenolic acids), are included in propolis. Caffeic acid phenethyl ester (CAPE), galangin, chrysin, nemorosone, propolin G, artepillin C, cardanol, cardol, pinocembrin, pinobanksin, chicoric acid, and ohenolic acids (as in ferulic acid, kaempferol, and coumaric acid) are among the main active ingredients in propolis. Other components include luteolin, apigenin, myricetin, naringenin, kaempferol, quercetin, polysaccharide, tannins, terpenes, sterols, and aldehydes. . 8 11 12 13 (Anjum SI, Ullah A, Khan KA, Attaullah M, Khan H, Ali H, et al,2019. Chiu HF, Yang CS, Chi HI, Han YC, Shen YC, Venkatakrishnan K, et al.,2017. , Hashemi JM 2016, Bae YJ, Lee EJ, Kang MH, Kwon OR, Kim MK, Sung MK. 2010)

Through modulation of various signaling molecules, propolis has been reported to exhibit potent anti-cancer/chemoprotective activity in many models (cell line/animal/human) of cancers of the head and neck, lung, liver, brain, pancreas, kidney, prostate, skin, breast, oral, esophageal, gastric, colon, and bladder. These comprise NF-κB, TSG (p53 and p21), lipoxygenase (LOX), inducible NOS, phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt), mitogen-activated protein kinases (MAPKs), metalloproteinases (MMPs), caspases, Bax/Bcl2, TNF-related apoptosis-inducing ligand (TRAIL), and nuclear factor erythroid 2-related factor 2/heme oxygenase will be among them. [11,16,17,19]. (Chiu HF, Yang CS, Chi HI, Han YC, Shen YC, Venkatakrishnan K, et al. 2017, Zabaiou N, Fouache A, Trousson A, Baron S, Zellagui A, Lahouel M, et al. 2017, Sawicka D, Car H, Borawska MH, Nikliński J 2012, Oršolić N. 2010) Numerous studies show that propolis has a wide range of therapeutic benefits, including anti-inflammatory, anti-microbial, antioxidant/free-radical scavenging, anti-cancer, anti-ulcer, anti-allergic, and anti-diabetic effects, in addition to hepatoprotective, cardioprotective, renoprotective, and dermaprotective (wound healing) qualities. [8,12,16]. (Anjum SI, Ullah A, Khan KA, Attaullah M, Khan H, Ali H, et al. 2019, Hashemi JM 2016., Zabaiou N, Fouache A, Trousson A, Baron S, Zellagui A, Lahouel M, et al 2017)

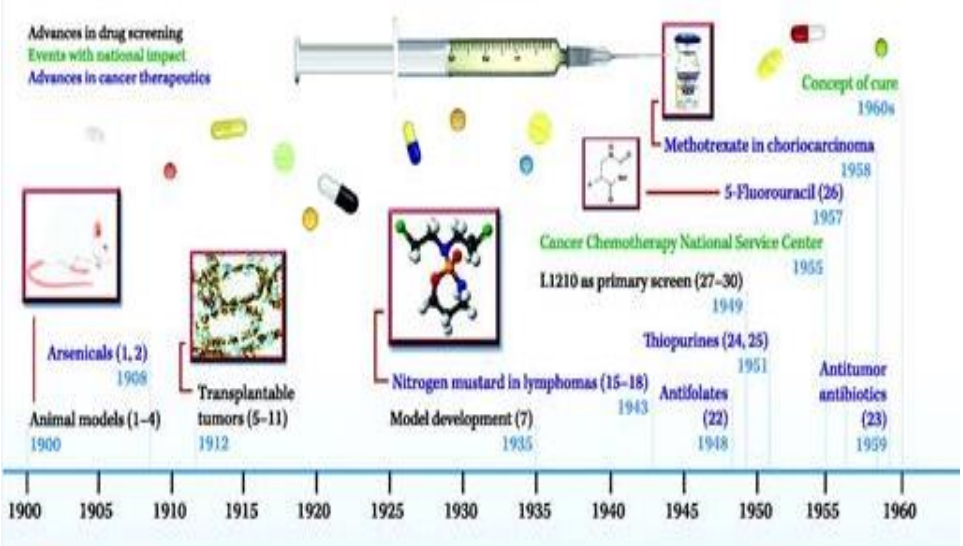
Effects of chemotherapy on melanoma, skin cancer, and dermal cancer, as well as underlying mechanisms

Much research has demonstrated, as in other sections, that propolis and its active phytocomponents exhibit a strong chemoprotective effect against melanoma or skin cancer in a variety of cell lines and animal models. 54 55 (Zheng Y, Wu Y, Chen X, Jiang X, Wang K, Hu F. 2018 , Ozturk G, Ginis Z, Akyol S, Erden G, Gurel A, Akyol O. 2012) Numerous studies demonstrated that propolis and its active ingredients could exhibit cytotoxic, anti-angiogenic, immunomodulatory, and anti-proliferative effects in different melanoma or skin cancer cell lines. [41,56,57]. (Kubina R, Kabała-Dzik A, Dziedzic A, Bielec B, Wojtyczka RD, Bułdak RJ, et al. 2015 , Pelinson LP, Assmann CE, Palma TV, da Cruz IBM, Pillat MM, Mânica A, et al. 2019, Kudugunti SK, Vad NM, Whiteside AJ, Naik BU, Yusuf MA, Srivenugopal KS, et al 2010) Through its inhibition of MMPs (matrix metalloproteinases) and stimulation of the NLRP1 inflammatory signaling pathway, propolis can cause apoptosis, cell cycle arrest, and autophagy. 54,58 (Zheng Y, Wu Y, Chen X, Jiang X, Wang K, Hu F. 2018 , Benguedouar L, Lahouel M, Gangloff SC, Durlach A, Grange F, Bernard P, et al 2016) have demonstrated that propolis and its active components (galagin)

initiate apoptosis and induce mitochondrial membrane potential loss through upregulating p38 mitogen-activated protein kinase (MAPK) and p62 as well as down-regulate tyrosinase activity (anti-melanogenesis) by modulating microphthalmia-associated transcription factor in B16F10 melanoma cells. Moreover, chrysin (an active ingredient of propolis) effectively stimulates apoptosis (Bax activation) by upregulating p38 MAPK and downregulating the ERK1/2 signaling pathway in A375 and B16-F1 melanoma cell lines 60 (Pichichero E, Cicconi R, Mattei M, Canini A.2011) (Chiu et al., 2020)

The Initial Phase of Cancer Drug Discovery

depicts a timeline and a portion of the history of the events leading up to the creation of cancer chemotherapy. Model development took up most of the first four decades of the twentieth century. The creation of models that might be used to efficiently narrow down the large chemical repertoire to the handful that might be active against human cancer was one of the two main obstacles to drug discovery. and second, the availability of clinical settings for the testing of such agents. Early in the 1910s, (George Clowes) of Buffalo, New York's Roswell Park Memorial Institute (RPMI) created the first transplantable tumor systems in rodents, which marked a significant advance in the field of model research. This development made it possible to test more compounds and standardize model systems. Finding the best model system for cancer medication testing was then the subject of intensive efforts, and it remained a key area of research for the following several decades. (Goldin A, Schepartz SA, Venditti JM, DeVita VT ,



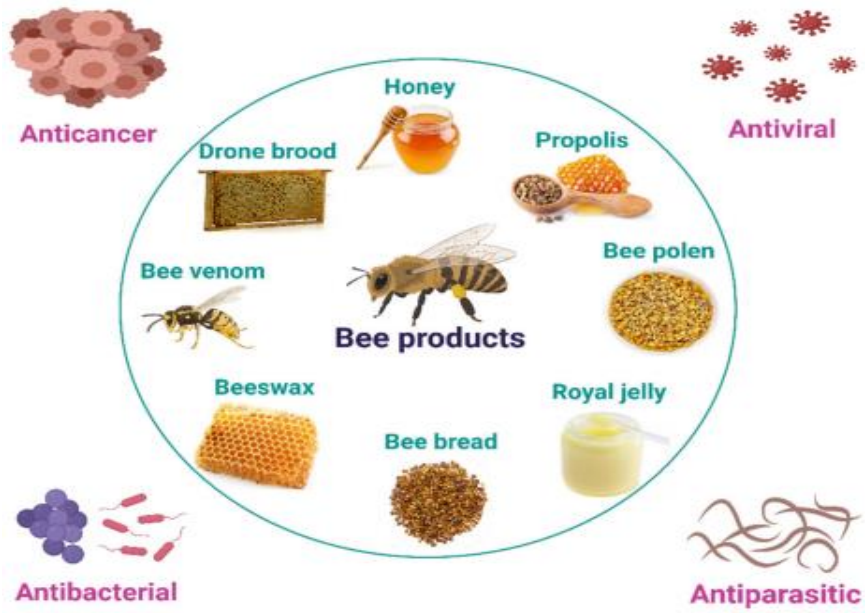
1979. p. 165–245 , Yoshida T , 1949) Sarcoma 37 (S37), Sarcoma 180 (S180),

Ehrlich's ascites tumor, Walker 256, and other early model systems were all mouse tumors caused by carcinogens (DeVita Jr and Chu, 2008)

Bee products and alternative cancer therapies

There is proof that bee products can be utilized to alleviate a number of ailments that cancer patients may experience while receiving therapy. Skin toxicity caused by radiation The effects of honey on skin toxicity caused by radiation therapy in patients with breast cancer were examined in two trials. According to both trials, honey and honey plus pentoxifylline together may be useful in preventing skin toxicity brought on by radiation therapy. 22-23 (Moolenaar M, Poorter RL , 2006 , 3. Shoma A, Eldars W, Noman N, et al ,2010) An earlier study demonstrated that pollen could, both objectively and subjectively, lower the frequency of side effects and boost the effectiveness of radiation. 24 (Hernuss P, Müller Tyl E, Salzer H, et al ,1975) (Münstedt and Männle, 2020) These days, biologically active bee products are becoming more and more popular because of their potential health benefits. Honey has been used for nutritional and therapeutic purposes for almost five millennia. 1 (Samarghandian, S.; Farkhondeh ,2017) As of right now, a number of honeybee products—including honey, pollen, royal jelly, propolis, beeswax, bread, and venom—have been found to be potential sources of compounds with medicinal potential for treating infections by various bacteria, viruses, and parasites as well as cancer. 3 (Cornara, L.; Biagi, M.; Xiao, J ,2017) Apitherapy frequently uses honey, pollen, bee venom, royal jelly, and propolis to treat a variety of cancers. Numerous studies have indicated that bee products show promise as cancer treatments. 5-7 (Münstedt, K.; Männle , H ,2020) (Rady, I.; Siddiqui, I.A.; Rady, M.; Mukhtar, H. Melittin ,2017) Research has verified that honey possesses oxidizing properties along with immune-modulatory, pro-apoptotic, anti-proliferative, anti-metastatic, and anti-inflammatory qualities. 6 (Afrin, S.; Haneefa, S.M.; Fernandez-Cabezudo, M.J ,2020) A gland in the bee's abdomen cavity produces and secretes bee venom, which is a biotoxin or apitoxin. It seems to be useful in the treatment of cancer, causing cytotoxicity, necrosis, apoptosis, and suppression of proliferation in a variety of cancer cells, such as those found in the bladder, prostate, liver, and breast. 7 (Rady, I.; Siddiqui, I.A.; Rady, M.; Mukhtar, H. Melittin ,2017) Bees gather propolis, sometimes referred to as bee glue, from green plants, shrubs, and tree buds. 3 (Cornara, L.; Biagi, M.; Xiao, J ,2017) It is composed of many chemical substances, including amino acids, polyphenols, minerals, flavonoids, ethanol,

vitamin E, vitamin B complex, and vitamin A, as well as essential oils, resins, pollen, and waxes. It combats viruses, bacteria, and other harmful microbes that invade hives. 10 (Anjum, S.I.; Ullah, A.; Khan, K.A.; Attaullah, M.; Khan, H.; Ali, H.; Bashir, M.A.; Tahir, M.; Ansari, M.J.; Ghramh, H.A.; et al. 2019) (Nainu et al., 2021)



Topical use of 5-Fluoracil

Nowadays, it is believed that queratosis actínica is not a precursor to escamocellular carcinoma but rather an early stage of the cancer, and the incidence of both escamocellular and basocellular carcinoma is continuously rising. El uso de agentes farmacológicos tópicos se enfoca en el manejo terapéutico del cáncer cutáneo no melanoma y de las lesiones precursoras. El siguiente artículo examina la variedad de farmacológicas tópicas disponibles hoy en día, debatiendo sus beneficios y drawbacks. These alternatives include imiquimod, retinoides, 5-fluoroacetate, diclofenaco, and photodynamic therapy. 5-Fluoracil has been the preferred topical treatment for actinic keratosis for a long time, ever since the US Food and Drug Administration approved it in 1970. (Lober B, Fenske N ,2004) It functions by preventing the production of DNA by inhibiting the thymidylate synthase enzyme. 5-fluoracil comes in a variety of

forms. It can be purchased as a 5%, 2%, or 1% solution or as a cream (Efudix 5%, Fluoroplex 1%, and Carac 0.5%). It is authorized for the management of superficial basal cell carcinoma, Bowen disease, and actinic keratosis. Actinic keratosis can be treated with a single application twice a day for two to four weeks, with an 82% clinical cure rate. In an effort to lessen adverse effects, alternative treatment approaches have been put forth; these include the use of pulsed therapy and topical steroids and/or antibiotics concurrently. 10 (Russo G., 2005) Some cases of in situ squamous cell carcinoma have also documented the effectiveness of 5% 5-fluoracil. The response to treatment in these skin cancer instances needs to be closely watched. Applying 5-fluoracil twice daily for seven to ten days prior to surgery has been found to be beneficial as a preoperative marker of the tumor margins in superficial tumors due to its local irritating activity. 7 (McGillis S, Fein H,2004)

Topical use of Diclofenac

Currently only approved for use in the United States of America, Solaraze is a topical gel formulation of 3% diclofenac in 2.5% hyaluronic acid, a nonsteroidal anti-inflammatory medication used to treat actinic keratosis. Although its exact mode of action is unknown, it has been demonstrated to impede the metabolism of arachidonic acid, which has an anticancer impact. For a duration of 60 to 90 days, it is used twice a day. Numerous research works have exhibited its effectiveness in managing actinic keratosis. 10,11 (Russo G. Actinic keratosis , 2005 , Gebauer K, Brown P, Varigos G ,2003) 47% of patients had full clearance of the lesions, and 77% had a notable improvement. 12 .13 (Rosso J. Lang P. ,2003) causing a slight to moderate amount of irritation, although far less than what happens when 5-fluoracil is applied. Additionally, reports of allergic contact dermatitis have been made. Its effectiveness in treating squamous or basal cell carcinomas has not been demonstrated to yet. Though it takes a long time to treat, it is thought to be a good therapeutic alternative that is easy to administer and has a higher chance of patient acceptance than 5-fluoracil. 7 (McGillis S, Fein H,2004)

Imiquimod

Immune response modulator imiquimod, found in 5% cream form (Aldara), has antiviral and anticancer properties. It stimulates the innate and cellular immune responses by causing the local release of interferon-alfa, tumor necrosis factor α, and other cytokines. Moreover, it has the capacity to trigger the death of tumor

cells. Not only is it licensed in Europe to treat superficial basal cell carcinoma, but it was recently approved to treat nonhyperkeratotic, Several research endeavors aimed at ascertaining the optimal treatment plans have demonstrated that an increased dosage yields a greater response, albeit at the expense of increased side effects. .14,15 (Rosso J. Jorizzo J. , 2005) (Barrera and Herrera, 2007)

Types of nano particle

Lipid-based NPs

Chapter 2

The aim of project:-

The purpose of this project is to find out the effect of some bee products on cancer cells and skin cancer.

Chapter 3

Martials and methods:-

Chapter 4 Results and discussion:-

Conclusions

Recommendations

Chapter 5

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