Role Of Pi3k/Akt/Mtor Pathways Behind Pathogenesis Of Skin Cancer: A Brief Review

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Abstract:

Skin cancer contributes to all most 30% of all newly diagnosed cancers in the world. Majorly two risk factors contribute to the pathophysiology of many skins carcinogenesis, which includes environmental (also called modifiable) and genetic (also called non-modifiable) risk factors. The most common environmental risk factor or trigger of almost all types of skin cancer is exposure to ultraviolet (UV) radiation. Despite the availability of a number of synthetic and natural compounds for treatment, there are clinical limitations to complete eradication. This has led to discoveries and research at the molecular level for a better understanding of cancer pathogenesis. At the molecular level, the mammalian or mechanistic target of rapamycin (mTOR) and associated phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt) pathways play a vital role in the regulation of cell growth, differentiation, migration, and survival, as well as angiogenesis and metabolism. It has found that downregulation of these pathways is correlated with genetic or epigenetic alterations, which is responsible for poor outcomes in a variety of human cancers including melanoma, squamous cell carcinoma and basal cell carcinoma. In this review we have summarized the role of PI3K/Akt/mTOR pathways behind skin carcinogenesis and the recent advancements in the development of nutraceuticals and synthetic small molecule targeting PI3K/Akt/mTOR.

Keywords: skin cancers; melanoma; squamous cell carcinoma; basal cell carcinoma; PI3K; Akt; mTOR; Merkel cell carcinoma; targeted therapy; nutraceuticals

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❖ Introduction:

Structure and Function of Human Skin:

Skin remains in the outermost region of human body and it is the largest body part that comprises nearly 20% of the complete body weight. In an adult human body, the skin counts near about 2 m^2 area on its surface level. The skin is placed at such a position that it defines the distinction between the internal and external environment (1). It looks quite ordinary if seen from the outside or from the surface level. But in reality, beneath the outer wall of the body, it presents various kinds of unique and complex biochemical features those which take part in forming the body via performing a lot of functions inside the same. The skin acts as a defensive, mechanical and physical shield to the threats coming from the external environment, such as – poisonous chemical agents, infectious microorganisms, ultraviolet (UV) radiation, as well as mechanical stressors (2-5). Not only in protecting from the outside threats, but also it controls the flow of inward and outward body fluids, such as – water, blood, sweats, electrolytes, and various other substances; takes an intermediary position in controlling immune and thermo-regulatory responses, coordinates sensory feelings and helps in metabolism in the energy storage unit of hypodermis (6-8). By the science of histology, skin is composed of three principal tissues of unique distinct features. The very first one is called Epidermis. It is positioned in the outermost area of the skin tissue. It's a non-vascularized, stratified, keratinizing squamous epithelium, with multiple layers whose density ranges vary from 75 & 150 µm in the interfollicular level and can go up to 600 µm in

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the palms and soles. The next one is the Dermis. This is comparatively a dense tissue enriched with collagen and elastin. This fibrous conective tissue is always flooded with blood and lymph vessels, nerve elements, and embedded with disseminated cells including fibroblasts, mast cells, macrophages, and lymphocytes. The third and last one in these components is Hypodermis, which is also called as Subcutaneous tissue. It lies underneath the Dermis. Fatty or Adipose tissues are the main components of Hypodermis. Blood vessels regularly transverse them.

❖ Different Layers of skin

• The Epidermis:

Epidermis, which stays in the most outer region of skin tissue, has a semi-permeable covering, works as the primary place of interaction with the external environment. In an adult body, the epidermis is constituted by more than 90% Keratinocytes, keratin synthesizing epidermal cells, a family of cytoskeletal scaffolding proteins that comes from different clan. They form 10-12 nm long intermediate filament networks that are made at different level of cornification (7). At those levels the functions that are made define the condition of the epidermis and make the skin impermeable. In the normal physiological state, an equilibrium is maintained between the regeneration and death of the keratinocytes, while the homeostasis is happening (9, 10). Other types of cells are also placed there in the enduring epidermis, such as – melanocytes, Langerhans Cells, and Merkel Cells, which plays just the same role as keratinocytes in maintaining the skin homeostasis process. Melanocytes are those cells which produce skin pigments and they're located at the dermal-epidermis junction and the hair follicles. Their main functions include synthesization of melanin with melanosomes, ensuring skin-pigmentation and photo protection and other biological regulatory and action including safety measures (11-15). Langerhans cells are the one who presents antigen which plays major role in the immune function of the skin and providing protective measures against external invaders and microorganisms (7,16-21). Merkel cells are mechanoreceptors which are oval in shape and plays major role in the sensitivity of light, touch (18). Based on skin site, histologically cross-section of skin shows that the epidermis is made of four (hairy or interfollicular skin) or five (palmoplantar or glabrous skin such as soles and palms) different cell layers or strata defined by various stages of keratinocyte maturation (Figure 2) (9,22). From the inside to the outermost surface of the skin, the layer which lies in the most deep of the epidermis is the basal or germinative cell layer (stratum basale; SB), which provides shelter to resident stem cells and their progenitor transient amplifying (mitotically active) keratinocytes. There are three different pools of keratinocyte stem cell. They are located at: 1) the basal compartment, 2) the tip of the dermal papillae, and 3) the hair follicle bulge that is attached to the basement membrane zone (BMZ) through hemidesmosomal protein complexes (6,22–25). The skin thus serves as a local storage of different populations of adult/multipotent stem cells, both in basal epidermal and dermal tissue compartments(9,24,26).Epidermal homeostasis is maintained by these multipotent stem cells from the hair follicle to the non-follicular skin, which have the ability to regenerate and differentiate multiple cell lines for epidermal, hair/non-hair follicles and sebaceous glands (27). During mitosis, the sister keratinocyte stem cell maintains a pool of stem cells, while the other pool of daughter cells keratinocytes divides asymmetrically into progenitor keratinocytes committed to the terminal differentiation (9,25,27). Once committed to differentiation, the progenitors are basal keratinocytes. They proliferate, separate and move towards the surface of the skin, gradually developing into spinous cells, granular and cornified layers in the process of cornification and are subsequently desquamated [9,28]. During cornification, as basal keratinocytes express keratin 5 (K5), keratin 14 (K14) and integrins uncoupling and up linking leads to several biochemical processes for keratinocyte gene expression differentiation-related markers such as keratins (K1,K10), filaggrin, loricrin, involucrin and transglutaminase (28,29). Overlying the basal layer is a spinous or spiny cell layer (layer spinosum; SS), which has a thickness of several layers and is characterized by an increased number of desmosomes. On top of this layer sits a layer of granular cells (stratum granulosum; SG), which contains about 3–5 cells layers surrounding lamellar bodies and keratohyaline granules [29]). Here the cells gradually flatten and collapse, which is associated with the

initiation of degradation of nuclei and other organelles, and active lipid and protein secretion. In places of the palmoplantar skin, the granular layer is covered by a clear layer (stratum lucidum, SL), which corresponds to the transition phase between the granular layer and stratum corneum, but SL is absent in the interfollicular epidermis, as discussed above. subsequently, the cornified or horny cell layer (stratum corneum, SC) is the outermost layer of the dermis this is made from three–10 layers of flattened corneocytes ranging 10–30 μm thick, in addition to intercellular lipids/protein complexes on the skin surface and gives the critical pores and skin barrier towards water loss and outside insults (7,30). The procedure of cornification culminates in the formation of the stratum corneum (SC), the remaining line of protection from the outside environment, which is composed of corneocytes, dead keratinocytes containing a highly specialized protein and lipid matrix and forms an essential part of the skin surface that offers the barrier (7,30). Corneocytes are finally lost through desquamation and replaced by way of newly differentiated cells, a process resulting within the regeneration of this tissue every 6–8 weeks in people and 8–10 days in mice (31). by readily diffusing via the intercellular layers, the SC may additionally permit the transportation of a few small, lipid-soluble compounds from the surface inwards into the pores and skin, and consequently, the integrity of the pores and skin as a dynamic organ is maintained via epidermal homeostasis. The equilibrium between epidermal keratinocyte proliferation and differentiation is tightly regulated, and deregulation of this stability is regarded as the cause of diverse pores and skin pathologies such as cutaneous cancers, and inflammatory pores and skin ailment.

- **The Dermis:**

underneath the epidermis present the mesodermally derived dermis (intermediate skin layer), a thick layer of dense connective tissue frequently together with the floor substance or extra cellular matrix (ECM) specifically made from collagen, elastin, fibrillin, and glycoproteins (non-structural) that provide the skin its suppleness and mechanical power (7,32,33). The dermis is comprised of essential layers: a) the papillary epidermis (superficial dermis), an intermediate layer rich in nerve endings, which is separated from the dermis by dermal-epidermal junction; and b) the reticulo-epidermis (deep and medium dermis), a elastic fibers containing dense connective tissue. The epidermis harbors blood vessels, hair follicles, nerve endings, sweat, and sebaceous glands that guide and nourish the dermis, and protects the vascular network and nerve fibers. The dermis additionally gives shelter plenty of various resident cell sorts, made of fibroblasts that synthesize collagen/ECM, those which are necessary for tissue elasticity, and histiocytes together with macrophages, lymphocytes and mast cells crucial in skin immune response.

- **The Hypodermis:**

The hypodermis or subcutaneous tissue is placed under the dermis (or subcutis). It contains adipose tissue, blood vessels, nerves and sometimes invaginations of epidermal appendages such as sweat glands, sebaceous glands, and hair follicles, those which enable the hypodermis in body insulation and functioning as an energy storage unit too (1,6) (Figure 1). Skin derivatives or appendages including the hair follicles, nails, sebaceous, sweat, and apocrine glands, those which are brought out from embryonic ectoderm are not present in palmoplantar or load bearing skin sites such as the palms and soles (6), as per the Figure 1. Though the skin differentiates in thickness based on the anatomical site, age, and the presence and density of derivatives, the fundamental structure is kept same at all body sites. All of the three skin tissues interact with each other via the secretion of immune-mediators, extracellular matrix proteins, growth factors and hormones (6,34). As it is a functional barrier, the skin is always in direct touch with the external environment. As because healthy skin is a must need in our physical appearance, it also plays a major role in our social and sexual encounters. Any kind of unnatural acquisition of intricate foreign particles leads to severe cutaneous diseases. Maximum of them are chronic and not much curable by treatment in nature.

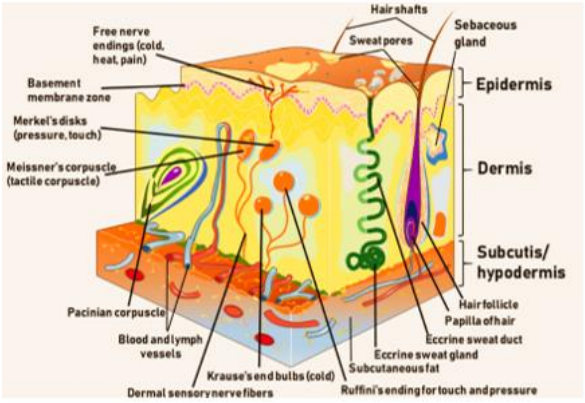

Figure 1: Schematic representation of different layers of skin

❖ Etiological Factors behind Cutaneous Carcinogenesis:

Majorly two risk factors contributes to the pathophysiology of many skin carcinogenesis, which includes environmental (also called modifiable) and genetic (also called non-modifiable) risk factors (18,35). The most common environmental risk factor or trigger of almost all types of skin cancer is exposure to ultraviolet (UV) radiation [36], that can be a cause of damage to DNA in skin cells such as keratinocytes and melanocytes. That results in tanned and burnt skin (35). As shown in (Figure 2), UV radiation builds the electromagnetic (EM) spectrum partially that reaches Earth from the sun. UV radiation lies between X-rays and visible light and are of three main types, UVA, UVB and UVC. They vary at different wavelengths ranging from 100 to 400 nanometers (nm) with different skin penetr-ating properties (37). In the measure of wavelength, UVA are the longest (320-400 nm). Then comes the UVB having medium wavelengths (290-320 nm) and at last comes the UVC (100-280nm). UVA rays aren't absorbed through the atmosphere (Earth's ozone layer), so they're transmitted through and can penetrate deep into the middle layer of the pores and skin through the basement membrane, in which the melanocytes reside to the superficial epidermis (38). UVB rays are almost definitely absorbed by the dermis (Figure 2). UVC rays are on the whole absorbed through the ozone layer and the atmosphere, to a point, this is regularly dependent on the climatic conditions (36,39). As a consequence, most of the UV rays that come in contact with the skin are UVA with a small amount of UVB (38). Both UVA and UVB exposures can result in a tanned skin appearance (37), and overexposure to UVB radiation causes erythema, swelling, and pain, the function signs and symptoms of sunburn, which normally take numerous hours to expand. Incident UV rays unto the skin can intermingle with several light-emitting pores and skin layer unique molecules to elicit each acceptable and unwanted results, contingent upon the UV rays' exposure, assets, and wavelength. appropriate effects include priming the pores and skin to synthesize vitamin D precursor as well as their consumption, in view of treating diverse cutaneous diseases inclusive of cancers (40–42). undesirable consequences of UV rays in pores and skin consist of allergic and inflammatory illnesses, immunosuppression, picture-growing older, oxidative pressure, carcinogenesis, and improved drug sensitivity (35,43–45). The molecular mechanism of UV-caused pores and skin cancers is associated with eliciting expanded DNA damage signals, e.g., activation of the p53 pathway and induction of the apoptotic pathway, which profoundly adjust cellular physiology to mediate cellular cycle arrest and prompt DNA restore (44,45). interestingly, exposure of human keratinocytes to UVA and UVB outcomes in activation of the phosphatidyl-inositiol 3-kinase (PI3K) as well as phosphorylation of Akt at S473 by way of UVB and at Thr308 by way of UVA in addition to expanded phosphorylation of the mammalian or mechanistic goal of rapamycin (mTOR) and p70 S6 kinase 1 (S6K1). Rapamycin pretreatment has been shown to suppress the expression of phosphorylated S6K1 upon publicity to UV radiation, and the silencing of Akt had no effect on its expression, an indication that publicity to UV radiation can prompt the PI3K/Akt/mTOR-S6K1 pathway (46).

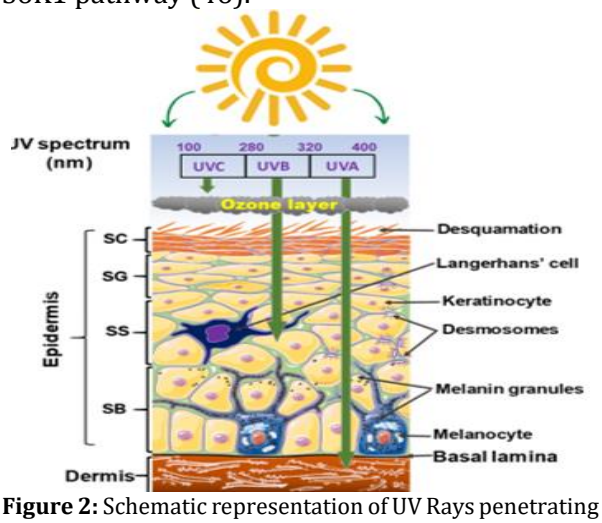

Figure 2: Schematic representation of UV Rays penetrating different layers of skin

❖ Different Pathways and their role in Tissue development & carcinogenesis (PI3K/Akt/Mtor):

In multicellular organisms, several signaling pathways are related to the law of gene expressions, therefore contributing to the organized complicated physiological procedures severely involved in skin cell increase, proliferation, survival, and differentiation, as well as pores and skin tissue development (47,48). Therefore, changes in those pathways can modulate protein synthesis, negatively impact skin cellular growth and proliferation, and result in phenotypically various skin sicknesses (47–49). Information of the intracellular alerts and mechanisms via which cells acquire and integrate extracellular cues is important for the prognosis and the improvement of novel and properly- focused healing regimen for resulting cutaneous malignancies. Among numerous signal transduction pathways, the PI3K/Akt/mTOR pathways (50,-51) are the hub involved in a diffusion of physiologic features linking boom elements, vitamins, and strength availability to lipid and protein synthesis, metabolism, mobile increase, proliferation, survival, apoptosis, angiogenesis, and tissue development (52,53). those pathways and associated components were regularly found to be down regulated in numerous cancers like melanoma and others cancers and are emerging as clinically relevant target (52,53).

❖ Structure And Functions Of Mtor Pathway:

whilst talking about mTOR, we've to mention rapamycin. Rapamycin (sirolimus) is an antifungal antibiotic that was first remoted from the bacterial strain Streptomyces hygroscopic us NRRL 5491 in 1975 [52,54] inside the soil of Rapa Nui Island (Easter Island) from which its call became derived (52). In 1991, hall laboratory first located target of rapamycin (TOR) in yeast [55,56]. until mid-Nineties, the mammalian counterpart (mTOR) changed into determined by Sabatini and colleagues (57). Rapamycin bureaucracy a complex with FK506-binding protein 12 (FKBP-12), after which the rapamycin-FKBP-12 complex binds to the FKBP-rapamycin-binding (FRB) area of mTOR, inhibiting mTOR function (50). consequently, mTOR is also termed FKBP-12-rapamycin-associated protein (FRAP), rapamycin and FKBP-12 target (RAFT1), rapamycin goal 1 (RAPT 1), or sirolimus effector protein (SEP). mTOR belongs to the PI3K-associated protein kinases (PIKKs) own family with a C-terminus that shares sturdy homology to the PI3K catalytic domain (figure 3). mTOR interacts with several proteins and forms at least exceptional complexes, particularly mTOR complex 1 (mTORC1) and a pair of (mTORC2), with wonderful kinase sports and mobile features (46,50,57). those complexes are big but have special sensitivities to rapamycin as well as one-of-a-kind effectors. each mTORC1 and mTORC2 share the subsequent common additives: Catalytic mTOR subunit, mammalian lethal with sec-13 protein8 (mLST8 or GβL), the terrible regulator DEP domain containing mTOR-interacting protein (DEPTOR), and the Tti1/Tel2 complex (reviewed in Reference (50)). The mTORC1 discretely accommodates the regulatory-associated protein of mTOR (Raptor), and every other poor regulator, proline-wealthy Akt substrate 40 kDa (PRAS40) . further to the above not unusual components, the mTORC2 moreover consists of the rapamycin-insensitive partner of mTOR (Rictor), the mammalian pressure-activated MAP kinase-interacting protein 1 (mSin1), and protein observed with Rictor 1 and a couple of (Proctor half of) (parent 4) (46,50,57). Both Raptor and mLST8 are high quality regulators of mTORC1's hobby and feature, while PRAS40 and DEPTOR are each poor regulators of the mTORC1 [46,52,58]. Raptor serves as a scaffold for recruiting mTORC1 substrates, while mLST8 binds the mTOR kinase area, and undoubtedly regulates its kinase activity. Then again, PRAS40 pals with mTOR through raptorto inhibit the interest of mTORC1, whilst DEPTOR capabilities as mTOR-interacting protein, to both mTORC1 and mTORC2, as a negative regulator in their activities (50,52).

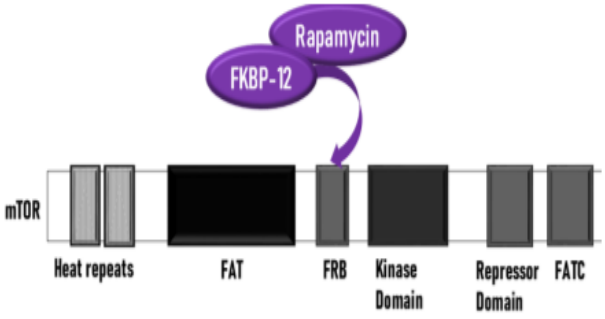

Figure 3. Different domains of Mtor

mTORC1 controls protein/lipid/nucleotide synthesis and lysosome biogenesis by mediating the phosphorylation of S6K1 and eukaryotic initiation factor 4E (eIF4E) binding protein 1 (4E-BP1) (parent protein 4), which is sensitive to rapamycin, growth factors, strength (ATP), nutrients (amino acids), oxidative stress, and DNA damage [50]. Akt, serum and glucocorticoid-inducible kinase 1 (SGK1), protein kinase C (percent), and focal adhesion proteins are all phosphorylated by mTORC2, which is only sensitive to extended (>24 h) rapamycin exposure in particular circumstances. It also affects the activity of small GTPases (46,57,59). Despite the fact that the characteristics of the m TOR complexes are yet unknown, recent studies suggest that m TOR is crucial for cell growth, proliferation, differentiation, survival, autophagy, and motility, as well as angiogenesis and lymph angiogenesis (46, 50, 57, 59).

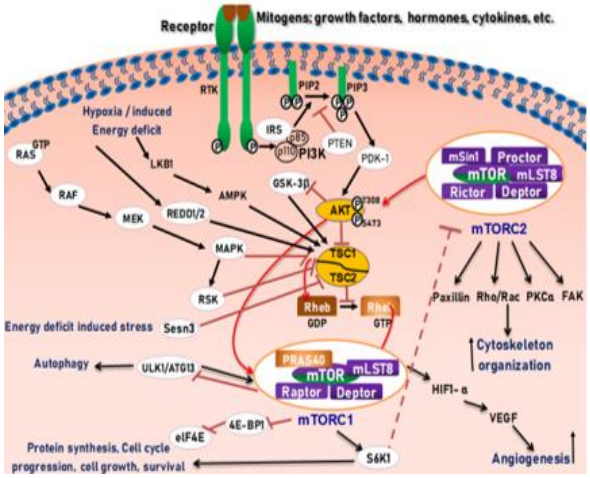

Figure 4: PI3K/Akt/mTOR signalling pathway diagram example. Inhibition is shown by bars, while activation is shown by arrows [50]. Insulin receptor substrate (IRS) stimulates phosphatidylinositol three-kinase (PI3K), which is then phosphorylated to produce phosphatidylinositol[3,4,5]-trisphosphate upon receptor activation (PIP3). To change the route of interest, Phosphatase and Tensin Homolog (PTEN) can dephosphorylate PIP3. PIP3 binds to the pleckstrin homology (PH) area on the amino terminal of AKT, activating it. This promotes the translocation of AKT to the plasma membrane, where the carboxyl terminal T308 is phosphorylated by phosphoinositide structured kinase 1 (PDK1) and the amino terminal S473 is phosphorylated by mTORC2. AKT regulates numerous mobile approaches inclusive of survival and mobile proliferation, through a selection of downstream proteins like glycogen synthase kinase three-beta (GSK-3β), Forkhead field O (FOXO), amid others (now not proven). AKT is able to at once phosphorylate and therefore inactivates the forty kDa proline-rich protein (PRAS40), relieving the suppressive law on mTORC1 hobby. furthermore, AKT can phosphorylate and inactivate the tuberous sclerosis (TSC) tumor suppressor protein complex that acts as a GTPase-activating protein (gap) for the RAS homolog enriched in mind (Rheb) small G protein to alter its interest. Retention of the Rheb-GTP bound form turns on mTOR, that's constituted of two foremost complexes that are related to diverse proteins inclusive of Raptor, mLST8, PRAS40 and Deptor for complicated I (mTORC1), and Rictor, mLST8, Deptor, mSin1 and Protor for complex II (mTORC2). mTORC1 is regulated by way of a variety of environmental indicators mediated through several proteins along with REDD1/2 (regulated in improvement and DNA damage responses half), AMP-activated protein kinase (AMPK), amongst others. mTORC1 phosphorylates downstream S6K1(p70S6 Kinase 1) and modulates the eukaryotic initiation thing 4E-binding protein (4E-BP1), which discharges it from hindering eIF4E, and enabling 40S ribosomal subunit to be recruited to mRNAs, leading to the initiation of protein translation. S6K also phosphorylates ribosomal protein S6 that is also worried in translational regulation with the aid of the 40s ribosomal subunit. through contrast, the regulation of mTORC2 continues to be beneath research, however it's far regarded to be regulated by way of increase elements. mTORC2 phosphorylates awesome businesses of proteins, permitting the regulation of actin cytoskeleton and migration through activating protein kinase C α (%-α), small GTPases (Rhoa, Rac1 and Cdc42), and focal adhesion proteins, inclusive of focal adhesion kinase (FAK) and paxillin. essentially, the activation of the RAS-RAF-MEK-ERK-RSK pathway mediated through increase component is some other mechanism of regulated crosstalk with the PI3K/AKT/mTOR signaling pathway.

❖ Regulation of PI3K/Akt/mTOR Pathways and role in Carcinogenesis:

mTORC1 is currently believed to be regulated via multiple routes (as will be discussed below), but it is still unclear how mTORC2 is regulated.

Currently, overexpression of PI3K leads to an increased mTORC2 activity, making it the most well-known upstream modulator of mTORC2 (figure 4). (46). The corresponding receptor, such as the insulin-like growth factor receptor (IGFR), platelet-derived growth factor receptor (PDGFR), or epidermal growth factor receptor (EGFR) at the cell surface, is activated in response to the binding of an increase factor and alerts to downstream molecules, activating multiple pathways, including PI3K-Akt, RAS-RAF, mitogen-activated protein kinase kinase (MEK)-extracellular signal-regulated kinas (57). The phosphatase and tensin homologue deleted on chromosome 10 (PTEN), a lipid and protein phosphatase, inhibits the activity of the activated PI3K, which catalyses the conversion of phosphatidylinositol (4,5) bisphosphate (PIP2) to phosphatidylinositol (3,4,5) triphosphate (PIP3) (figure 4). PIP3 facilitates Akt docking to the cell membrane by binding to the pleckstrin homology (PH) domain of the serine/ threonine kinase. There, Akt is phosphorylated by mTORC2 on S473 and by phosphoinositide-established kinase 1 (PDK1) on T308 (46). As a result, Akt can be positively controlled by PI3K and negatively regulated by PTEN (46,50, 57,59). Therefore, constitutive activation of Akt/mTOR, which has been observed in numerous malignancies, is caused by a loss of PTEN and/or PIK3CA mutations (52).

TSC1 (also known as hamartin), TSC2 (also known as tuberin), and TBC1D7 combine to form a complex that functions as a GTPase-activating protein (gap) for the Ras homolog enriched in brain (Rheb) GTPase (46,50,57,59). Rheb interacts with mTORC1 to potently increase its kinase activity in its GTP-sure state (46,50,57,59). The TSC1/2 complex, which is a Rheb gap, adversely controls mTORC1 by switching an active GTP-bound Rheb into an inactive GDP-certain state [50]. To prevent TSC2 from establishing a complex with TSC1 in response to growth factor stimulation, the activated Akt can phosphorylate TSC2 at S939 and T1462, which leads to the retention of the active (GTP-certain) Rheb kingdom and the activation of mTORC1 (46,50,57,59) (figure 4). Be aware that Akt can also activate mTORC1 by phosphorylating PRAS40, which causes PRAS40 to separate from raptor, in a TSC1/2-independent manner (50). In actuality, the TSC1/2 complex can also communicate stronger signals to mTORC1. Increased aspect stimulation causes the active ERK1/2 and ribosomal S6 kinase 1 (RSK1) to swiftly phosphorylate TSC2 at the residues S664/540 and S1798, respectively. This inhibits the TSC1/2 complex and, as a result, activates mTORC1 (46,50,57,59). IKK is induced in response to the pro-inflammatory cytokine tumour necrosis factor (TNF), which may phosphorylate TSC1 at S511/487, inhibiting TSC1/2 and activating mTORC1. Furthermore, considering that GSK3 is normally responsible for the phosphorylation (S1371, S1375, S1379, and S1387) and activation of TSC2 through GSK3 inhibition of glycogen synthase kinase 3 (GSK3) and mTORC1 through TSC1/2 (46,50,57,59).

Furthermore, hypoxia-induced tumour suppressors REDD1 and/or AMPK can activate the TSCl/2 complex, blocking the mTORC1 signalling pathway [46,50,57,59]. AMPK is an AMP-activated protein kinase. The RAS is a very highly controlled intracellular signalling route for cellular growth and survival. The RAS is activated when complexed with GTP, and Neurofibromatosis Type 1 (NF1), a protein that causes Neurofibromatosis Type 1 when mutated, inhibits the conversion of GDP to GTP (57). As was previously established, RAF and MEK are downstream of activated RAS, and they have an impact on the activation of ERK1/2 and RSK1 (46,50,57,59). TSC2 can be specifically phosphorylated by the active ERK1/2 and RSK1, which inhibits the TSC1/2 complex and activates mTORC1 (figure 4). Consequently, the PI3K–Akt and RAS–RAF–MEK–ERK–RSK pathways both work together to modulate the mTORC1 signalling (46,50,57,59).

As a result, through the activation of S6K1, 4E-BP1, lipin1, activating transcription factor 4 (ATF4), transcription factor EB (TFEB), Unc-51 like autophagy activating kinase 1 (ULK1), hypoxia-inducible factor 1 (HIF1), and other proteins, mTORC1 also regulates energy metabolism, protein/ lipid/ nucleotide synthesis, lysosome biogenesis, autophagy Review in (53) and for further information (50,57,59). Through an interaction between Raptor and a TOR signalling motif in S6K and 4E-BP1, activated mTORC1 specifically phosphorylates S6K1 and 4E-BP1. S6 (40S ribosomal protein S6) is phosphorylated by

activated S6K1, which improves mRNA translation. In contrast, this similarly promotes translation and activates the transcriptional components of RNA polyme-rases I and III, resulting in the creation of ribosomes, tRNAs, and translational elements (57,59). However, by binding to and deactiv-ating the eukaryotic translation initiation factor 4E (eIF4E), 4EBP1 acts as an inhibitor during the commencement of translation (50,57,59). 4E-BP1 will separate from eIF4E when it is phosphorylated by mTORC1. The released eIF4E can eventually link to eIF4G and eIF4A to form the eIF4F complex, which binds the 5' cap of mRNAs and encourages eukaryotic translation initiation (46,57,59).

Little is known about the upstream activators of the mTORC2 pathway, in contrast to mTORC1. So far, it is believed that mTORC2 responds to cues from growth factors, such as insulin, through direct connections to the ribosome in a PI3K-based manner (46,50,57). By phosp-horylating Akt at its hydrophobic motif (S473) and SGK1 (S422), a kinase that regulates ion transport and boosts Akt, mTORC2 activates Akt right away (46,50,60). Although the absence of mTORC2 totally abolishes the activity of SGK1, it no longer prevents the phosphorylation of other Akt targets, such as TSC2 (46,50). As a result, in addition to encouraging mTORC2's association with ribosomes, PI3K also regulates the activation of mTORC1 through the regulation of Akt-structured TSC1/TSC2, as previously ment-ioned. It has been hypothesised that PI3K encourages mTORC2 to attach to ribosomes, which instantly activates mTORC2, and that mTORC2 phosphorylates Akt at S473 to activate Akt (50,57).

Extended (>24 h) treatment with rapamycin or rapalogs has been shown to decrease mTORC2 assembly by disrupting the rictormTOR complex and subsequently decreasing Akt signalling, despite the fact that mTORC2 is expected to be less responsive to rapamycin (46,58). In other words, the insulin receptor substrate 1 (IRS1) is immediately phosphor-rylated by S6K1, which encourages IRS1 breakdown and downregulation of PI3K/Akt (46,50,58). Researchers have discovered that treating cancer cells with rapamycin or its analogues can cause the activation of PI3K/Akt through the S6K1-IRS negative feedback pathway, reducing the capacity of cancer cells to undergo apoptosis (46,50,58). This has turned out to be one of the factors contributing to the inadequate clinical anticancer activity of rapalogs. Additionally, mTORC2 controls the mobile actin cytoskeleton and migration by activating the small GTPases Rhoa, Rac1, and Cdc42, as well as focal adhesion proteins such focal adhesion kinase (FAK), paxillin, and protein kinase C (p.c). As a result, mTORC2 has the ability to control cellular growth, proliferation, survival, and motility (46,58). (determine 4).

❖ Dysregulation of PI3K/Akt/mTOR Path-ways and Cutaneous Cancer:

Numerous severe human malignancies, include-ing many types of skin cancer, have been linked to deregulated PI3K/Akt/mTOR pathways [46,52]. This has ultimately led to the development of specific PI3K, Akt, and mTOR inhibitors for targeted cancer therapy (reviewed in References [46,52,57]). As previously mentioned, UVA and UVB exposure contributes to the development of skin cancer and is linked to the dysregulation of the mTOR pathway [46,50,52,57]. It has been established that aberrations caused by modifiable (UV) and non-modifiable (genetic) distresses in the target genes or proteins of the intracellular networks controlling skin homeostasis lead to a wide range of phenotypically diverse, and overla-pping, cutaneous malignancies. Skin cancers, such as melanoma and non-melanoma skin cancers, but not only those, are characterised by tissue neoplastic and hyperplastic growth (basal and squamous cellular carcinoma, Merkel cellular carcinoma[46,52,57]).

Since the molecular causes and goals of the majority of skin malignancies are well established, novel development and effective administration of chemotherapeutic drugs targeted at the malfunction closer to mainta-ining skin tissue homeostasis and integrity are potential treatment modalities [46,50,61,62]. On this mild, a number of synthetic small molecule drugs and evidently continuing nutraceuticals have been shown to modify the activities of PI3K/Akt/mTOR and can thus serve as novel therapeutic choices for those cutaneous tumours [46,50]. Below, we discuss the importance of the PI3K/Akt/mTOR pathways, effector molecules, and various skin maligna-

ncies. We also discuss the molecular role of several synthetic compounds and dietary phytochemicals in suppressing those processes as potential therapeutic approaches.

❖ Role of PI3K/Akt/mTOR as a novel target for Melanoma Skin Cancer:

Skin cancer known as melanoma is brought on by the malignant alteration of epidermal melanocytes (63,64). Under the two major categories of skin cancer , Melanoma and Non-melanoma are the two. Under which melanoma accounts for less than 1% of all incidences of skin cancer. But due to its potential for metastasis, this kind of skin cancer is roughly 75% responsible for all deaths associated with skin cancer (63,65). According to the American Cancer Society's cancer statistics, there were around 178,560 melanoma cases in the US in 2018. Within which, 87,290 cases are localized, non-attacking, and only affect the epidermis. However, the remaining 91,270 cases are the exact opposite of them and spread from the epidermis to the dermis. Melanoma-related deaths were predicted to affect 9320 persons in the same year (5990 males and 3330 women). This one fact, which is imposed in addition to the well-known risk factors for melanoma development and the decreasing 5-year survival rates of 12–28% depending on the site of metastasis in patients with melanoma, is also a result of the rising socioeconomic burden of the disease (63, 64, 66). The radial growth stage (RGP), a horizontal lesion with a plaque-type appearance on the upper epidermis, is frequently the initial stage of primary benign melanoma. From there, the lesion progresses to the vertical growth stage (VGP), an infiltrative stage that gradually metastasizes, frequently to major organs like the lungs. Increased Akt/mTOR activity has been documented in about 70% of metastatic melanomas, and it has been suggested that this activity is what causes the conversion from RGP to VGP (63,67). We recently have found that Akt functions as a molecular switch connected to mTOR, S6K1, enhanced angiogenesis, and concurrent peroxide generation that also promotes aggressiveness in metastatic melanoma using a melanoma model. (68).

❖ PI3K/Akt/mTOR and Associated Pathways as a novel target for Chemotherapeutics, Biologic Drugs, Natural Products, and Synthetic Derivatives in Melanoma:

One of the strongest aids to the development of melanoma has been thought to be activation of the mTOR pathway (63, 64, 66, 69). Autophagy of cell is inhibited and the normal cell cycle is dysregulated by constitutive mTOR activation (70). The development of novel medications, such as rapalogs (deforolimus , everolimus, and temsirolimus) and other inhibitors of mTOR kinase that target this signalling system has been facilitated by advances in our understanding of the molecular genetics of melanoma.

❖ Chemotherapeutic Synthetic Molecules & Biologic Drugs:

Different preclinical *in vitro* and *in vivo* studies have demonstrated that dual PI3K/mTOR inhibitors has shown significant inhibitory activity on cell proliferation and Akt activation, some of which have been investigated in clinical trials in patients with normal mTOR mutation (63). Several synthetic molecules mechanistically targeting PI3K/Akt/mTOR and related RAS/RAF/MEK/ERK or MAPK signaling pathways and have been shown to be potential therapeutics for metastatic melanoma. (63). Other drugs, such as the BRAF inhibitor vemurafenib & dabrafenib and its MEK1/2 inhibitor trametinib in a patient with metastatic melanoma resulted in long-term survival in (63). In addition, combination therapy with dabrafenib and trametinib better outcomes in patients with metastatic melanoma alone. A combined approach /mTOR (but especially PI3K), MAPK, and other signaling pathways with additional compounds that specifically target them have been investigated in several clinical trials (63).

In addition, BRAF serine/threonine kinase mutation is found in almost 50% patients with malignant melanoma; in more than 90% of cases, BRAF contains the V600E point mutation (72). A mutation in BRAF activates the MAPK pathway, which is involved in the survival of cancer cells and proliferation. BRAF inhibition is also a promising approach in the treatment of malignant melanoma. And many small molecules have been introduced to inhibit BRAF, some of which are approved FDA targeting BRAF mutated malignant melanoma.

However, resistance to such molecules it is quite common to lead to therapeutic failure. A number of mechanisms contribute to leakage BRAF inhibition has been reported in several studies. One of the studies reported this involvement of hepatocyte growth factor (HGF) in the acquisition of resistance to BRAF inhibitors through upregulation of c-MET and GAB1, leading to activation of the MAPK pathway (73). Abnormal expression of long non-coding RNAs (lncRNAs) is also involved in metastatic growth cells in many types of cancer. Activation of c-MET lncRNAs KCNQ1OT1 [74] or downregulation tumor suppressor microRNA MiR-22 from MALAT1 (75) and miR-152–3p from HOTAIR (76) found to increase the metastatic growth of melanoma cells (74). Treatment of melanoma cells with a combination of the BRAF inhibitor Vemurafenib and the c-MET inhibitor AMG 337 (73) or siRNA therapeutic benefits in BRAF mutant malignant melanoma. Hersey et al. announced that clinically, it has been a combination of synthetic chemotherapeutic molecules and targeted biological therapies beneficial in distant metastatic disease (71).

Rapamycin, a specific mTORC1 inhibitor, inhibits cell growth and proliferation as shown in several melanoma (77,78). Also two other rapamycin analogs, everolimus and temsirolimus showed promising results in preclinical studies, induced cytostatic inhibition of tumor growth and reduction of angiogenic capillary perfusion. However, everolimus failed in a phase II clinical trial demonstrate adequate efficacy in the treatment of patients with metastatic melanoma; but it is anti-angiogenic role suggested potential use in combination therapy (79). Another mTOR inhibitor, temsirolimus in combination with temozolomide had a significant effect reduced tumor growth and increased apoptotic death in melanoma cells that showed resistance to the BRAF inhibitor vemurafenib [80]. In a phase I clinical trial, the combination of temsirolimus and autophagy inhibitor hydroxychloroquine, accelerated cell death in melanoma (81).

Hainsworth et al. observed that the combination of bevacizumab and everolimus was well tolerated and had moderate activity in treating patients with metastatic melanoma in a phase II trial by the Sarah Cannon Oncology Research Consortium [82]. This suggests that additional research into substances with similar modes of action, when combined with pharmacological inhibitors of secondary signalling pathways, is a worthwhile field of study [82]. In the animal model, VS-5584, a small molecule drug, is well tolerated and demonstrates excellent pharmacokinetic qualities. It is a powerful, highly selective new human PI3K and mTOR dual inhibitor. Shao et al. showed strong and concurrent blocking of the activated His component of Akt/mTOR signaling and downregulation of cyclin D1 expression in melanoma, suggesting effective His PI3K/mTOR dual inhibition because melanoma is very resistant to traditional chemotherapeutic drugs. It has demonstrated utility as a tool [67,84-86]. Additionally, the efficacy of VS-5584, when taken orally, inhibited the growth of A375 melanoma xenografts in naked mice. The clinical evaluation of VS-5584 in melanoma patients, as well as that of ABT-737 and other targeted inhibitors, was justified by the co-administration of VS-5584 and ABT-737 (a Bcl-2 inhibitor), which further potentiated the suppressive effect. elucidate the purpose for the creation of In Auxiliary Settings [67].

A novel chalcone with the 2,2 dimethyl benzopyran motif, called SKLB-M8, was developed from the millepachin (MIL) found in traditional, flavonoid-rich Chinese medicine and Millettia pachycarpa Benth (Leguminosae). A modified MIL derivative known as (E)3(3-amino4-methoxyphenyl)1 (5-methoxy2,2-dimethyl-2H-chromen-8-yl) prop-2-en-1-one hydrochloride (SKLB-M8) has been shown to have anti-tumor action, particularly against melanoma. In melanoma models, Wang et al. reported that the SKLB-M8 therapy reduced the activity of the activated Akt/mTOR signalling pathway, produced G2/M arrest, and promoted apoptosis. It also reduced angiogenesis by inhibiting the activation of ERK1/2[87,88].

The basement membrane-associated NC1 domain of collagen type XIX [NC1 (XIX)] was employed by Oudart et al. as a multi-objective strategy because it is more advantageous than a single-objective strategy. A 19-amino acid peptide found in numerous targets near the C-terminal end of the 1 chain (XIX) identification in the fight against melanoma [89]. Using the NC1 domain in tumours Oudart et al. were able

to target the v3 integrin contact using collagen type XIX [C1(XIX)]. shown that PI3K/Akt/mTOR and FAK pathways, as well as migration and invasion, were inhibited in melanoma cells and a melanoma preclinical model [89–91].

Another azole molecule with FDA approval, itraconazole is a member of the antifungal medication class family and has been redesigned to treat several malignancies, including melanoma[110,111]. Itraconazole has been shown to have antimelanoma properties in a study by Liang et al. [110]; this study also revealed that the PI3K/mTOR and Hedgehog /Wnt pathways are inhibited as part of the molecular mechanism.

An increasing body of research has linked abnormal miRNA (microRNA) expression to the development of melanoma, particularly uveal melanoma (UM) [114,115]. In melanoma cells, RNA-binding motif protein 47 (RBM47) is the target of miR-25, which also activates the PI3K/Akt/mTOR signalling pathway, according to Jiang and Liu's research [116]. Meng and co. Recently, clinical evidence showed that patients with malignant melanoma had dramatically increased miR-138 levels. Via controlling the expression of PDK1 through the PI3K/Akt/ mTOR autophagy pathway [117]. Furthermore, a study by Li et al. revealed that miR-224-5p decreased PIK3R3/AKT3-targeted uveal melanoma (UM) cells' proliferation, migration, and invasion, indicating that miR-224-5p restrained the proliferation, migration, and invasion of UM patients. and a focus for diagnostics [115]. Additionally, Micevic et al. showed that in a Braf/Pten mouse melanoma model, deletion of overexpressed DNA methyltransferase (DNMT3B), which plays a protumorigenic role in human melanoma, led to a substantial suppression of melanoma formation [118]. This loss also triggers hypomethylation of the miR-196b promoter and a rise in miR-196b expression, which directly targets Rictor (a subunit of mTORC2) and prevents mTORC2 from being activated, which is crucial for the development and growth of melanoma. To do. Thus, via influencing mTORC2 signalling, this study proves that DNMT3B is a regulator of melanoma formation and suggests a potential therapeutic target for melanoma [118]. Additionally, because aggressive and highly metastatic cutaneous melanoma overexpresses Rictor, the master regulator of Akt phosphorylation, there is a direct correlation between Rictor inhibition and liver metastases in melanoma mice. Through interactions between cancer cells and cancer-associated hepatic stellate cells (HSCs), Schmidt et al. reported for the first time that mTORC2 /Rictor plays a crucial role in melanoma liver metastasis. Schmidt et al. also found that inhibiting mTORC2/Rictor significantly reduced Akt phosphorylation and cancer cell motility. The activation of both mTORC1/2 is necessary for Braf-induced melanomagenesis, according to Damsky et aldiscovery .'s that mTORC1 activation prevented BrafV600E induction growth arrest but was inadequate to halt melanoma formation [120].

Targeting the primary mTOR pathway in melanoma cells has been studied with rapamycin, its analogues, and other protein kinase inhibitors. In order to understand the role of rapamycin (mTOR), everolimus (mTOR), U0126 (ERK1/2), LY294002 (PI3K), CHIR-99021 (GSK-3), and other compounds in human VGP (WM793) and metastatic (Lu1205) melanoma cells, Cioczyk-Wierzbicka et al. found these compounds' antiproliferative properties [121]. Temsirolimus (Torisel), which reduces the growth of melanoma in vivo, targets multiple cancer-related hallmarks. Everolimus (RAD001), an oral active rapamycin analogue, was previously shown to provide potential benefits for the treatment of metastatic melanoma (NCCTG-N0377, Alliance). However, a phase II investigation revealed that severolimus alone did not exhibit sufficient anticancer efficacy, indicating that it should be investigated in combination with other medications in future clinical studies [79]. Si et al. showed that mTOR inhibitors had minimal effect in an unselected group of melanoma patients, while a sizable number of Melanoma patients with mTOR mutations responded better in a recent phase II study of everolimus vs advanced melanoma patients with mTOR mutations [92]. The study hypothesised that it could be possible to select appropriate patients who would respond to therapy with mTOR inhibitors in future prospective studies (clinical trial information: NCT01960829). Everolimus (RAD001) was recently the subject of a phase II multiinstitutional trial by Rao et al. (DOI: 10.1200/jco.2006.24.18 suppl.8043) to

evaluate its effectiveness in treating patients with metastatic melanoma. From the ongoing investigation of 20 patients, they deduced that RAD 001 was well tolerated and had adequate antimetastatic effectiveness against melanoma. The outcome encouraged them to start accepting participants for the trial's second phase.

Se,Se′1,4phenylenebis(1,2ethanediyl)bisisoselenourea, also known as PBIT [S,S′1,4 phenylenebis (1,2ethanediyl) bisisothiourea], is an isosteric analogue of the iNOS inhibitor that has been used most effectively as a tiny molecular component in the fight against melanoma's systemic (122). According to recent research by Chung et al., PBISe temporarily inhibits activated Akt signalling while concurrently activating the ERK1/2 pathway, preventing the development of cutaneous melanocytic lesions or melanoma up to 70%–80% in a reconstructed melanoma skin model and close to 50% in a mouse melanoma tumour xenograft. The study finds that the PBISe therapy, which simultaneously targets both pathways, has the ability to prevent the growth of cutaneous metastatic melanoma in skin [102].

Perifosine, an Akt inhibitor and alkylphosphocholine analogue, failed to demonstrate its efficacy in the phase II clinical trial. Additionally, it exhibited a number of negative side effects and biochemical toxicity, which made it abundantly evident that no further research is being done on this particular molecule for treating recurrent melanoma in humans [105,123].

In vitro and in vivo studies on the mouse model have shown that PI103, a kinase inhibitor focused on class I PI3K and both mTORC1 and mTORC2, has very minimal anti-proliferative and cytotoxic effects when used alone. However, Werzowa et al. demonstrated that the combination of PI-103 and rapamycin synergistically produced apoptosis and decreased Akt/S6 protein phosphorylation with advanced efficacy in opposition to malignant cancer both in vitro (in cancer cells) and in vivo (in a melanoma animal model) [104].

❖ Natural Plant-Derived Extracts, and Phytochemicals and their Synthetic Derivatives:

Additionally, natural dietary phytochemicals have produced encouraging anti-proliferation, anti-invasive, and anti-metastatic effects in a variety of cancer forms, including melanoma. These benefits are frequently linked to their capacity to target PI3K/Akt/mTOR and additional signalling pathways involved in the development of melanoma (melanomagenesis). Since many of these natural phytochemicals are less toxic and have less adverse effects at physiologically feasible dosages, investigating their potential for use singly, in combination, or as adjuvants to this vast array of established anticancer targets is a commendable therapeutic opportunity. A non-exhaustive list of cases that have been successful in treating melanoma is provided below.

Acacetin (5,7-dihydroxy-4′-methoxyflavone) is a naturally occurring flavonoid that is obtained from the black locust, Robinia pseudoacacia [124, 125]. It has been shown to have antioxidant, anti-inflammatory, and anticancer effects. The regulation of the PI3K/Akt/IKK, MLK3/MKK3/6 and p38 MAP kinase pathways has been linked to its anticancer action (reviewed in Reference [124]).

Jung et al. reported that acacetin inhibited PI3K activity, suppressed Akt phosphorylation, and significantly regressed SK-MEL-28 melanoma tumour growth in vivo, suggesting an anti-melanoma agent. They did this using cell-free, biophysical, computational, cell-based, and in vivo melanoma xenograft models (124).

The active ingredient in chilli peppers known as capsaicin(trans-8-methyl-N-vanillyl-6-nonenamide) has been shown to prevent B16F10 melanoma cells from migrating and forming new blood vessels in vitro [126]. This was accomplished by blocking the PI3K/Akt/Rac1 signal pathway.

A significant natural alkaloid present in Evodiae fructus is evodiamine. Human melanoma A375S2 cells were treated with evodiamine, which caused cell death via the PI3K/Akt/caspase and Fas/L/NF-B signalling pathways [127]. This result was amplified when the proteasome's function was inhibited.

An organic flavonoid known as isoliquiritigenin (ISL) has been shown to have both in vitro and in vivo anticancer action. The A375 melanoma cell was strongly suppressed by ISL therapy. Through lowering the protein expression levels of activated mTORC2AktGSK3 signalling pathway components, researchers were able to inhibit melanoma growth, induce G2/M cell cycle arrest, upregulate signs of terminal melanocyte differentiation, and drastically reduce melanoma cachexia. ISL and Ku0063794 (a mTOR-specific inhibitor) were administered together, and this boosted the markers of melanocyte differentiation and synergistically suppressed proliferation [128].

The primary active component of bee venom (BV), melittin, is an amphiphilic short peptide with 26 amino acid residues that has been shown to have anti-inflammatory, antibacterial, and anticancer properties. Melittin and BV have been shown to have antimelanoma effects through mechanisms linked to the inhibition of the PI3K/Akt/mTOR and MAPK signalling pathways. Further evidence that melittin may be a promising anti-melanoma drug comes from the fact that melittin and temozolomide (TMZ; chemotherapeutic agent) greatly decreased melanoma cell growth and invasion when compared to the two agents acting alone [129].

Boesenbergia rotunda's rhizome contains a phytochemical called panduratin A, which has been reported in numerous studies to be helpful against various cancer types. It has been demonstrated in a recent study to cause autophagic cell death in melanoma cells that are resistant to chemotherapeutics that induce apoptosis. Panduratin A was discovered to induce autophagy through the inhibition of the mTOR signalling pathway [130].

Yet another complex Chinese herbal remedy Traditionally, the compound Muniziqi granule (MNZQ), which comprises 13 medicinal herbs, has been utilised to treat endocrine disorders. Acne, chloasma, dysmenorrhea, menopausal syndrome, and melanoma that are caused by disorders. Peganum harmala plant seed extract, which contains the carboline alkaloid harmine, is one of the ingredients of MNZQ. In mouse B16 melanoma cells, harmine has been reported to cause apoptosis and autophagic cell death. The suppression of several signalling pathways, including the Akt/mTOR and ERK1/2 signalling pathways, led to the induction of autophagy [131].

The major active ingredient of the medicinal plant Sinomenium acutum, sinomenine (7,8-didehydro-4-hydroxy-3,7-dimethoxy-17-methylmorphinane-6-one), has also been found to induce apoptosis and reduce proliferation in B16 melanoma cells and animal tumour xenografts. By blocking the PI3K/Akt/mTOR signalling pathway, sinomenine induces autophagy, which has antiapoptotic and antiproliferative effects [132].

Prodigiosin and obatoclax, two small compounds belonging to the prodiginines family, have been shown in studies by Espona-Fiedler et al. to have an anti-melanoma action that is related to the inhibition of both mTORC1 and mTORC2. Notably, prodigiosin and obatoclax had no effect on T308 but hindered Akt phosphorylation at S473 [133].

A dietary bioactive flavanol called fisetin (3,7, 3′, 4′ tetrahydroxyflavone) is widely distributed in fruits and vegetables with colour, such as persimmons, apples, cucumbers, onions, and According to reports, strawberries have pleiotropic effects on a variety of human ailments, including tumours [134–136]. Treatment of cutaneous cancer with fisetin has been studied, in particular Melanoma with constitutive Akt/mTOR signalling activation caused by PTEN mutations, TSC1/2 or PIK3CA [77,137,138]. According to Syed et al., fisetin targeted a number of important melanoma-genesis indicators by a variety of pathways, including Akt/RSK/mTOR/S6K inhibition fisetin is a powerful anti-melanoma agent, according to the axis [68,139,140]. Pal et alinvestigation .'s of the Effects of fisetin alone and when combined with sorafenib in therapy showed that fisetin improved In athymic nude mice that were xenografted with a tumour, sorafenib caused apoptosis and prevented tumour growth. Through the suppression of the expression of activated components of in melanoma cells with BRAF mutation Pathways PI3K and MAPK [141]. According to the data, simultaneous inhibition of PI3K and Fisetin and sorafenib together may provide a more effective melanoma treatment by targeting MAPK pathways.

Turmeric's polyphenolic active ingredient, curcumin (diferuloylmethane), which is derived from the plant Curcuma longa's rhizome, has demonstrated a wide range of health benefits, including anti-inflammatory, antioxidant, and pro-apoptotic effects in various cancers by modulating multiple signal transduction pathways. Zhao et al. reported the induction of autophagy and concurrent inhibition of proliferation and invasion by suppressing activated components of the Akt/mTOR signalling pathway in human melanoma cells after treatment with curcumin [142]. Another investigation by Rozzo et al. revealed that a curcumin analogue (D6) dramatically reduced melanoma cell proliferation and triggered apoptosis via downregulating the PI3K/Akt and NF-B pathways [143].

It has been demonstrated that resveratrol (trans-3,5,4-trihydroxystilbene), a naturally occurring bioactive phenolic compound found in pigmented fruits like cranberries, grapes, and peanuts, has a variety of biological and health-promoting effects by focusing on a number of disease-related molecular markers [144,145]. Resveratrol treatment of B16 melanoma cells led to the induction of autophagy through a mechanism involving the formation of ceramide and inhibition of the Akt/mTOR pathway, indicating a possibility for treating melanoma, as demonstrated by Wang et al. [144,146]. Additionally, in malignant melanoma and fibroblast cell lines, resveratrol therapy decreased cell migration and invasion and inactivated Akt/mTOR effectors, according to Bhattacharya et al. [46,145]

Recent research has demonstrated the potential of honokiol, a natural phenolic chemical that has been utilised for a very long period in Chinese and Japanese traditional medicine. Honokiol therapy induced cytotoxicity and cytostatic effects by suppressing the Akt/mTOR and Notch signalling pathways in malignant melanoma cancer cells, according to Kaushik et alresearch .'s (63,147).

The most prevalent catechin in green tea (Camellia sinensis), epigallocatechin 3-gallate (EGCG), has demonstrated various health benefits, including anticancer potential. In specifically, EGCG inhibits PI3K and various signalling pathways, including Reference, to have pharmacological effects in vitro and in vivo on the migration and/or metastasis and on the management of melanoma. [148]

NexrutineR, a product of Phellodendron amurense, stimulates oxidative stress while suppressing the antioxidant response. Agents that target these can stop the disease because melanoma cells have an elevated oxidative stress profile that contributes to increased protein damage, oxidised glutathione, reactive oxygen species (ROS), and KEAP1/NRF2 pathway activity as compared to normal melanocytes [149]. According to Hambright et al., treatment with NexrutineR increased the levels of oxidative stress markers that are already elevated, decreased proliferative activity, survival rates, and colony formation in melanoma cells, and was linked to the selective inhibition of PI3K/Akt/mTOR pathway activation [149,150].

❖ PI3K/Akt/mTOR as Target for Treatment of Basal Cell Carcinoma:

The two primary types of non-melanoma skin malignancies are basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC), which together make up keratinocyte carcinoma (KC) (NMSC)[151-153]. Among Caucasians or ethnic groups with blue or green eyes, blond or red hair, and light-colored skin exposed to the sun for extended periods of time, BCC is the most prevalent kind of non-melanoma skin cancer [154-157]. Up to 80% of skin cancers and almost 30% of all malignancies diagnosed in the US are basal cell carcinomas (BCC), which have an incidence rate of up to 5% per year and a total yearly cost of about $400 million [160]. BCC develops in the basal epidermal cell layers. BCC often does not pose a life-threatening hazard, but if ignored, it can result in disfigurement and loss of function [159–164]. The presence of a cluster of tumours in the dermal layer is one of the morphological characteristics of BCC. Layer of the skin made up of cells that resemble undifferentiated basal epidermal cells cellularly. The palisade arrangement of epidermal cells in the tumour periphery, which divides the tumour from the surrounding stroma, is a significant characteristic of BCC. These cells frequently give the tumour its nodular appearance or create a band or string around it. The primary risk factor for BCC is direct sunlight exposure (UVA and UVB radiation), which is dependent on the rate,

extent, and duration of exposure to UV irradiation. Tumor cells differ from their normal counterparts in that they have less cytoplasm and a chromatin-rich nucleus, which results in more frequent mitotic division. However, apoptotic cell death also accounts for the slow progression of the tumour [165] discussed above. Immunosuppression, trauma, arsenic poisoning, and other skin conditions including Gorlin-Goltz syndrome or xeroderma pigmentosum are additional risk factors for BCC [166,167].

BCC can present clinically in a variety of morphological ways, including nodular or cystic, superficial, infiltrating, sclerotic, or pigmented, each of which has a unique site of occurrence. The superficial BCC typically develops in the trunk, but the nodular or cystic BCC typically manifests as lone, glossy, red nodules on the face. The most aggressive kind of tumour, infiltrating BCC, frequently has a less distinct boundary [155, 165]. Although various non-canonical pathways such WNT, NOTCH, p53, and the P13K/Akt/mTOR pathways have been implicated in the pathogenesis of BCC, upregulation of the Hedgehog signalling has been proven to be the main mechanism of BCC formation.

It was shown by Po-Lin So et al. that even a brief suppression of the PI3K/Akt/mTOR pathway can maintain the prevention of BCC carcinogenesis for a considerable amount of time after therapy is finished [106]. This indicated that short-term exposure of BCCs to PI3K inhibitors can lead to chemotherapy or chemoprevention, avoiding the toxicity and adverse effects that frequently accompany long-term use of other anticancer drugs such tazarotene [106]. Everolimus (an mTORC1 inhibitor) exhibits antiproliferative efficacy against various different neoplasia types, but especially against BCC. In BCC patients with partial or total disease regression, an oral daily dose of 1.5–3 mg everolimus has shown considerable improvement [93]. Because the P13K/Akt/m- TOR pathway, p53, WNT, Hedgehog, NOTCH, and other signalling pathways interact with one another in BCC, it is common to develop resistance to a certain pathway inhibitor. Assuming that combination therapy with inhibitors of the value of several signalling pathways has been established. The effectiveness of the treatment for BCC is currently being investigated with the PI3K inhibitor buparlisib in combination with the smoothened (SMO) inhibitor erismodegib [166]. Additionally, there is a lot of crosstalk across various routes, resulting in a complex web of molecules that confers resistance to medications that target a specific signalling [93]. The Hedgehog pathway's GANT61 (inhibitor of GLI) has been tested to see if it may effectively target BCC. However, the resistance to Hedgehog signalling inhibitors has evolved due of the interaction between PI3K and Hedgehog signalling. In a rhabdomyosarcoma model, it has been demonstrated that PI103 and GANT61, two PI3K/mTOR inhibitors, work together to synergistically overcome resistance [166]. To ascertain the efficiency of the SMO inhibitor erismodegib in BCC, buparlisib, another PI3K inhibitor, is being studied [166]. Retinoids are reported to be beneficial in human BCC carcinogenesis at pharmacological dosages. It has been demonstrated that the retinoid tazarotene inhibits murine BCC by blocking the IGFR/PI3K/Akt/mTOR signalling pathway [106,107].

Through the discovery of new pharmacological effects of the existing pharmaceuticals with documented therapeutic activity, drug repurposing has assisted in the identification of newer anticancer medications. In the 1980s, the antifungal drug itraconazole was revealed to have anticancer effect by suppression of many signalling pathways, including Akt/mTOR, Hedgehog signalling, and Wnt/catenin signalling. Itraconazole has been discovered to bind to the voltage-sensitive anion channel in mitochondria and interfere with ATP synthesis, hence inhibiting mTOR signalling. Recent clinical trials for the treatment of BCC with itraconazole showed encouraging results, and these trials are still underway [168]. Retinoids are reported to be beneficial in human BCC carcinogenesis at pharmacological dosages. The RARs (retinoic acid receptors) α, β, and γ, bind the retinoic acid produced by the natural conversion of retinoid to retinoic acid and slow the development of BCC carcinogenesis in the endodermal layer of the skin. One noteworthy example is the prodrug tazarotene, which, when transformed into the anticancer agent tazarotenic acid, may potently bind and activate RAR and receptors [106,107].

❖ PI3K/Akt/mTOR as Target for Treatment of Cutaneous Squamous Cell Carcinoma:

The clinical appearance of cutaneous squamous cell carcinoma (cSCC), which accounts for about 20% of NMSCs and is the second most common non-melanoma skin cancer worldwide after BCC including but not limited to the development of nodular masses, hyperkeratotic plaques, and skin ulcerations that may be accompanied by pain, itchiness, or bleeding [170]. The premalignant forms of cSCC Actinic Keratosis AK and Bowen's illness [171] both progress to malignancy if untreated. Although 95% of cSCC may be surgically treated to cure them, 20% of skin cancer fatalities are thought to be caused by cSCC [172]. The local lymph nodes and the dermis layer nearby are two places where the cSCC can spread. It has been discovered that lymph node metastasis occurs in about 5% of patients [173]. The main factor contributing to the development of cSCC is exposure to UV radiation from sunlight. Other causes include radiotherapy used to treat other skin disorders like psoriasis and occupational exposure to ionising radiation. It has also been discovered that immunosuppressive medication followed by organ transplantation may have contributed to the development of cSCC. Patients who receive the immunosuppressant azathioprine for an extended period of time have an increased chance of developing cSCC [174].

Since cSCC has been found to overexpress EGFR, targeting EGFR has been a viable therapeutic strategy in the management of this kind of cancer. Gefitinib, an EGFR tyrosine kinase inhibitor, demonstrated a positive outcome in patients with aggressive cSCC of the head and neck in a phase II clinical investigation [175]. Furthermore, compared to other non-melanoma skin malignancies, particularly BCC, cSCC has been shown to demonstrate a higher degree of mTOR activity [176,177]. Although cSCC exhibits more aggressive behaviour than BCC, it is interesting to note that because these cell types have higher mTOR levels, they respond more favourably to mTOR inhibitors [178]. Comparing cSCC to its premalignant forms, AK and BD, an elevated mTOR level was also seen. This form of cancer also showed increased expression of cyclin-dependent kinase 2 (CDK2), indicating a connection between it and the Akt/mTOR pathway. Along with mTOR, this may serve as an additional therapeutic target for the treatment of cSCC [179]. Rapalogs (such as sirolimus, everolimus, etc.) can be effective treatments for patients since they suppress the immune system while still having antiproliferative activity. For these characteristics, these m TOR Inhibitors play a major role in battling cancer after receiving an organ transplant. Rapalogs have reportedly shown promise in treating post-transplant skin cancers, particularly cSCCs [180]. A new orally bioavailable PI3K/mTOR dual inhibitor called LY3023414 is now undergoing phase I/II clinical trials for the treatment of people with cSCC, according to a recent study [112-113]. In a study comparing actinic keratosis (AK) and squamous cell carcinoma (SCC) acquired by laser capture microdissection, Einspahr et al. used reverse phase protein microarray analysis and found that the MEKERK, EGFR, and mTOR pathways were abnormally activated [181]. In a different study, Chen et al. found that CDK2 expression was highly linked with frequent constitutive activation of the Akt/mTOR pathway components in predominantly malignant epidermal cancers, suggesting that this system causes the malignant transformation through CDK2 in epidermal tumours [179].

In head and neck SCC, the PI3K/Akt/mTOR signalling pathway has been linked to the emergence of EGFR drug resistance. Therefore, in a phase II clinical trial to treat head and neck SCC, everolimus (a mTORC1 inhibitor) and erlotinib (an EGFR inhibitor) were combined. Unfortunately, patients with metastatic cancer did not see any clinically significant improvements from this combination treatment [182].

Alkyl phosphocholine erufosine, also known as erucylphospho-N, N, N-trimethyl propylammonium, demonstrated promising anticancer effects in oral squamous cell carcinoma. The downregulation of the mTOR signalling cascade by erufosine led to the promotion of apoptotic and autophagic cell death as well as an antiproliferative impact [94].

To treat cSCC, a number of small compounds have been created that target mTOR signalling. Ex vivo tests on several of these compounds have produced encouraging findings. A brand-new small chemical called GDC-0084 exhibited strong inhibitory effects on both mTORC1 and mTORC2. It had cytotoxic and antiproliferative

effects on a number of established and primary cSCC cell lines. GDC-0084 has been proposed as a potential therapeutic drug for the treatment of cSCC after a clinical research in human subjects shown its good safety and tolerability as well as the complete shutdown of the PI3KAktmTOR signalling cascade [95]. A different PI3K/mTOR dual inhibitor, LY3023414, has demonstrated strong cytotoxic effect against a number of cSCC cell lines as well as tumour xenograft models when used in vivo. High aqueous levels LY3023414 is positioned as a possible chemotherapeutic drug for the treatment of cSCC due to its oral bioavailability and solubility. Phase I and II clinical trials for this small chemical are now being conducted [112].

❖ PI3K/Akt/mTOR as Target for Treatment of Merkel Cell Carcinoma:

As a deadly nonmelanoma skin cancer of neuroendocrine origin, Merkel cell carcinoma (MCC), which Toker originally identified in 1972, contains neurosecretory granules with an abnormally high level of 1500 cases each year on the gloomy rise in the US alone. An age-adapted incidence of MCC is increasing annually by 8% in Australia and other regions of the world, compared to only 3% for cutaneous melanoma, according to five-year epidemiologic data. A mortality rate of 46% was related with metastatic disease in about 50% of MCC patients, which is significantly higher than the melanoma mortality rate [109]. Despite this rise, patients with AIDS have been observed to have an estimated 11-fold higher number of MCC cases. Epidermal stem cells give rise to the electron-dense neuroendocrine granules that contain Merkel cells [183]. The pathophysiology of MCC, which most frequently affects the head and neck and other sun-exposed parts of the body, is still not fully understood.

As a potential cause of MCC, Merkel cell polyomavirus (MCV) was identified in 2008. This finding suggests that integration of the viral genetic material into the cell is what causes virus-induced pathogenesis. Various publications have described the molecular mechanism underlying this pathogenesis, which involves p53, PTEN, Ras/MAPK, and PI3K/Akt. According to a recent study, MCC cells may be affected by activated Akt/mTOR and its downstream effector molecules p4EBP1 (S65) and pS6K [109]. Additionally, a study found a positive correlation between the MCV-specific T cell antigen and the translation initiation factor 4EBP1 to support the idea that MCV-positive tumours may also be affected by activated Akt/mTOR signalling [184]. Additionally, it was demonstrated that constitutive 4E-BP1 activation that was prevented from being phosphorylated disrupted the MCV-specific T cell transformation activity, indicating that 4E-BP1 inhibition (phosphorylation) is necessary for MCV transformation [109, 184]. More research has revealed that Akt is hyperphosphorylated in MCC whether or not MCV is present [109, 184].

Even while first-generation mTOR inhibitors like rapamycin and other rapalogs are now being studied in a variety of cancer types, including several cutaneous malignancies, there are currently no effective treatments for MCC. Second-generation mTOR inhibitors with the ability to target both mTORC1 and mTORC2 have been created in response to the decreased efficacy of rapalogs brought on by feedback activation of Akt. For instance, the mTORC1 and mTORC2 inhibitor MLN0128 has the ability to effectively reduce the growth of MCC in both in vitro culture and in vivo mouse xenograft models. For the treatment of MCC, MLN0128 is now conducting a phase II clinical trial and is about to begin a dose escalation procedure [98,99].

In 24 hours, WYE 354, an allosteric mTOR inhibitor, was found to be more effective than Ku 006394 at increasing autophagy in primary human MCC cell lines routine [109].

NVP-BEZ235 is a second tiny molecular target of the PI3K/Akt/mTOR pathway that interferes with the ATP-binding site of PI3K and mTOR kinase to limit its activity. It is an oral bioavailable derivative of the imidazoquinoline. NVP BEZ235 is now undergoing a phase I clinical study for solid tumours after showing promise in a number of preclinical studies against osteosarcoma, glioblastoma, breast, prostate, and pancreatic cancer. It has been discovered that this substance causes cell cycle arrest and inhibits the proliferation of MCC cells in culture. Dual inhibition of PI3K and mTOR was discovered to be a component of NVP BEZ235's anti-cancer cell proliferation mechanism [101].

❖ PI3K/Akt/mTOR as Target for Treatment of Tuberous Sclerosis:

Known to affect people of many races, especially those from sub-Saharan Africa or black and of African descent, tuberous sclerosis complex (TSC) is an inconsistently expressed, primarily autosomal dominantly inherited neurocut-aneous syndrome/disorder that affects the skin, brain, kidneys, eyes, and other organ systems [185,186]. Pathologically, TSC is characterised by benign, non-invasive, tumor-like lesions or organ hamartomas, which manifest in a broad spectrum of clinical consequences. These commonly manifest as hypomelanotic macules, confetti skin lesions, facial angiofibromas, shagreen patches, fibrous cephalic plaques, or ungual fibromas in the kidneys, lungs, central nervous system, and skin [187–189]. TSC gene mutations change cell proliferation and differentiation at the genetic level, resulting in tumours, hamartomas, or altered neuronal polarity. According to reports, the majority of people with TSC abnormalities exhibit specific phenotypes linked to attacks, such as childhood spasms associated with autism and varying intellectual disability [188,190]. TSC is typically thought to be a rare condition with an average frequency of 1:6000 live births and a prevalence of 1:14,000 to 1:25,000 [189,191]. More than 85% of TSC cases are thought to be caused by mutations in one of the two tumour suppressor genes, TSC1 (encoding hamartin) or TSC2 (encoding tuberin) [192]. Through the mTORC1 -enabled biosynthesis pathways, hamartin and tuberin are triggered in aberrant circumstances to prevent substrate consum-ption. Importantly , malfunction of hamartin or tuberin occurs in people with TSC due to mutation of either TSC1 (on chromosome 9) or TSC2 (on chromosome 16). Due to the stimulation of the mTOR signalling, abnorm-alities in cell cycle progre-ssion, transcription, translation, and metabolic regulation ensue from the downstream kinase signalling cascade [193,194]. The categorization of mosaic forms of TSC into subclasses based on illness prognosis and severity allowed for the identification of phenotypic differences. They described patients with mosaic disease who had bilaterally symmetric facial angiofibromas, asymmetric facial angiofibromas, and germline TSC affecting both cutaneous and internal organs [186,195,196]. Heart failure caused by intracardiac rhabdomyomas can occur in some newborns, and age typically affects how likely it is that they will develop renal angiomyolipomas. Renal illness is the second-leading cause of early death due to TSC, with central nervous system tumours serving as the primary cause of morbidity and mortality [189]. Recently, the pathogenesis of TSC as well as its clinical diagnosis and therapeutic therapy have been examined [191]. A multidisciplinary approach was agreed upon as being necessary for the best care of TSC patients [188]. Currently available options for treatment and care are conservative and include surgery, pharmacologic treatment with mTOR inhibitors, biologic therapy (such an anti-EGFR antibody), and ultrasound-guided percutaneous microwaves are among recent proposals [191]. The significance of topical applications/indication of mTOR inhibitors and evaluation of their efficacy and safety in dermatologic disorders, including TSC, was covered in a recent review accompanied with meta-analysis that included a total of 262 patients in 40 trials [197]. The study found that out of 262 patients, about 157 often had angiofibromas connected to TSC, and that topically applied mTOR inhibitors such sirolimus were well tolerated and more effective against angiofibromas than a placebo [197]. Everolimus (Afinitor) has been approved by the FDA for the treatment of specific types of brain and kidney tumours brought on by TSC [198], and there is greater hope that this may be used in the future to eliminate cutaneous tumor-like lesions and manage systemic diseases.

❖ Conclusions, Clinical Implication, & Future Prospects:

The majority of cutaneous malignancies have well-understood molecular bases and targets, which have diagnostic and therapeutic benefits, because they will enable the development of novel, safer, less expensive, and more effective chemotherapeutic agents, biological inhibitors, and natural dietary agents that target the dysregulation of different biological pathways to maintain skin tissue homeostasis and also the integrity of skin. Targeting these systems with therapeutic naturally-synthesized bioactive phytochemicals, biological compounds, and synthetic small molecules alone or as various combination therapy is a viable approach to treating skin malignancies because the PI3K/Akt/mTOR signaling plays a significant role in skin carcinogenesis. Several of the synthetic previously mentioned compounds

have so far being widely used in clinical studies as prescription drugs. The majority of these medications have known drawbacks and undesirable side effects, necessitating careful consideration and the creation of stronger, more practical, and safer treatments [199–201]. The capacity of synthetic and natural compounds to treat PI3K/Akt/mTOR-associated cutaneous illnesses has been thoroughly investigated [202,203]. Despite predictions that the global market for nutraceuticals research will reach a milestone of $340 billion by 2024 (Variant Market Research, Pune, India), there is currently no evidence to support the existence of synthetics and their analogues. High throughput drug screening and recent technology advancements in *in-vitro* and *in-vivo* animal illness models will hasten the identification and development of anticancer drugs. Some of the existing inhibitors are being studied in early-stage clinical studies for the treatment of skin-related cancers, thus more research is necessary.

CONFLICT OF INTEREST:

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS FOR THE CREDIT WORK:

SR and CV designed the study's overall structure. The study was carried out by SR and CV. The data and contradictions in the data were examined by SR and CV. SR first drafted the article, which was then amended by CV, after data confirmation.

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