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HYBRID NANOTECHNOLOGY FOR HYPERPIGMENTATION: INTEGRATING NANO EMULSION AND METALLIC NANOPARTICLES FOR MULTIFUNCTIONAL MELANIN REGULATION

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Abstract:
Hyperpigmentation is a persistent and multifactorial skin disorder characterized by excessive melanin deposition and associated with melasma, post-inflammatory hyperpigmentation, solar lentigines, freckles, and photoaging. Conventional depigmenting agents and procedures are often limited by poor skin penetration, instability, irritation, recurrence, and inconsistent efficacy. This review evaluates the potential of nanotechnology, focusing on nano emulsions, metallic nanoparticles, and hybrid nano emulsion metallic nanoparticle systems for improved management of hyperpigmentation. The molecular mechanisms of pigmentation are discussed, with emphasis on tyrosinase, microphthalmia-associated transcription factor, tyrosinase-related protein 1, tyrosinase-related protein 2, melanocortin 1 receptor signaling, cyclic adenosine monophosphate signaling, mitogen-activated protein kinase signaling, and Wingless-related integration site/β-catenin signaling, together with the roles of oxidative stress, inflammation, melanosome biogenesis, and melanosome transfer. Nano emulsions can enhance solubilization, stability, skin permeation, bioavailability, and controlled release, whereas metallic nanoparticles provide antioxidant, anti-inflammatory, ultraviolet-protective, and melanogenesis-modulating effects. Their integration may improve dispersion, delivery, retention, stability, and targeting while reducing irritation. Future directions include artificial intelligence-assisted formulation, personalized nano therapy, exosome-mediated delivery, stimuli-responsive systems, advanced skin models, green nanotechnology, and clinical translation. However, further research is required to establish long-term safety, optimize particle characteristics, validate efficacy through clinical studies, and facilitate reproducible manufacturing, regulatory approval, and successful commercialization for broader therapeutic and cosmetic applications.

Keywords: *Hyperpigmentation; Nano emulsion; Metallic nanoparticles; Melanogenesis; Tyrosinase inhibition*

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1.INTRODUCTION

One of the most prevalent skin disorders in dermatological practice is hyperpigmentation, characterized as localized or generalized accumulation of excess melanin causing dark pigmentation[1]. Although traditionally treated as a cosmetic problem, disorders related to skin pigment deposition represent major causes of suffering from a psycho-emotional point of view, and often interfere with self-confidence and the general quality of life[2]. The global incidence of skin pigmentary alterations is steadily increasing, with chronic exposure to environmental elements such as ultraviolent (UV) radiation, environmental pollution, hormonal imbalances, natural ageing processes, inflammatory skin diseases and genetic factors as principal contributing factors[3]. The most prominent clinical presentations are melasma, post-inflammatory hyperpigmentation (PIH), solar lentigines, freckles (ephelides), and age pigmentation, all major targets in daily clinical practice and particularly challenging from therapeutic standpoint due to their chronic and recurring nature[4]. In people with Fitzpatrick skin type III–VI, persistent skin hyperpigmentation constitutes an important therapeutic target in daily dermatological care and is relevant for the public health[5]. Skin pigment deposition, often known as melanogenesis, is highly orchestrated by and biologically regulated by a physiological cascade of signals responsible for the protection of cell DNA from UV radiation, primarily driven by the interaction between melanocytes, keratinocytes and melanosomes-which together comprise epidermal melanin unit[6]. Specifically, a carefully orchestrated series of enzymic processes inside melanosomes, managed by the tyrosinase (TRP-1) and tyrosinase (TRP-2) coordinated activation via microphthalmia-associated transcription factor (MITF) integrating several different signal transduction pathways-e.g.–MC1R/cAMP/PKA/CREB, MAPK, PI3K/Akt as well as the Wnt/-catenin pathways– maintain adequate skin pigmentation level[7]. Nevertheless, overuse and over-activity, resulting from the exposure to UV irradiation, oxidative stress, inflammation, alteration in endogenous hormonal signals, and genetic susceptibilities, contribute to uncontrolled activation of melanogenic enzymes with excess melaninization of the epidermis, triggering hyperpigmentation[8]. Of the diverse triggers associated with pigmentary disorders, the excessive formation of reactive oxygen species (ROS) through environmental factors such as UV radiation and pollution as well as skin damage resulting in inflammation that leads to impairment of native cellular antioxidants systems followed by enhancement in signal transduction pathways which in turn activates tyrosinase has been recently identified as the most prevalent molecular culprit[9]. Alongside the excess ROS production, inflammatory mediators such as tumor necrosis factor alpha (TNF-), interleukin IL-)1 and 6 trigger melanocyte stimulation and prolong and facilitate the chronic pigmentation development[10].Hence, recent investigations suggest a multifactorial nature of hyperpigmentation comprising oxidative stress, inflammation, melanosome development and transfer of melanosomes, in addition to over-activated tyrosinase, which has recently become the central part. By the evidence based on growing knowledge on mechanism, novel multifunctional therapeutic strategy targeting multiple molecular mechanisms of hyperpigmentation has become the most recent paradigm[11]. So far, the treatment of hyperpigmentation has mainly relied upon topical depigmenting ingredients such as hydroquinone, kojic acid, azelaic acid, arbutin, retinoids, niacinamide, vitamin C, and tranexamic acid combined with procedural treatments like chemical peels, laser, intense pulsed light (IPL) and microneedling[12]. In spite of several studies showing beneficial therapeutic outcomes, topical and cosmetic treatments still have many drawbacks, including poor aqueous solubility of some of these ingredients, insufficient skin penetration, low bioavailability, chemical instability and poor solubility in aqueous medium, fast degradation, more frequent administration, skin irritation and allergic contact dermatitis, appearance of ochronotic after persistent usage and relapse of pigmentation after removal of therapeutic agents[13]. The treatment cost and a risk of post-inflammatory hyperpigmentation of dark skin tones associated with procedural techniques further limit clinical applications[14]. In these context of limitations it is vital to identify novel delivery vehicles such as nanoparticles, improve stability of these compounds and enhancing the penetration through epidermal stratum corneum.[15] Emerging new approaches through application of nano-vehicles have remarkably improved treatment outcome of these persistent pigmentary issues as such formulations enhance skin permeability[16]. Nanoparticles deliver encapsulated bioactive molecules, improve the penetration of topically applied depigmenting agents through barrier function of the skin, sustain the release, and protect vulnerable compounds from rapid degradation[17]. As such they have become a breakthrough approach for the cosmetic

management of dyschromia. The nanoparticles system based formulations have a greater surface to volume ratio and are used in different shapes and form including liposomes, solid lipid nanoparticles, polymeric micelles and others[18]. Nano emulsions, a class of thermodynamically stable emulsions with particle sizes varying between 20 and 200 nm, have long been reported to exhibit remarkable properties such as great skin permeation capabilities, ability to encapsulate various drugs (lipophilic and hydrophilic), large interfacial surface area, stability over a wide range of concentrations and shear forces, as well as reduced irritancy of the drug[19]. They have been widely adopted in various dermatological application. The unique physicochemical and biological properties of metal nanoparticles have recently attracted considerable attention owing to their inherent ability to combat the multifactorial nature of pigmentary disorders[20]. Silver nanoparticles (Ag NPs), gold nanoparticles (Au NPs), ZnO NPs, TiO NPs, ceria nanoparticles (Ce NPs), Selenium NPs, copper (II) oxide nanoparticles (Cu NPs), and polymeric metallic hybrid nanoparticles offer a multimodal mechanism for tackling pigmentation through direct tyrosinase inhibition, down regulation of MITF and MITF targeted downstream genes, reduction of ROS, inflammation, and UV-induced damage, and interruption of melanogenesis in melanocytes[21]. By contrasting with conventionally used depigmenting agents that typically affect a single target, metal nanoparticle are involved in regulation of multiplicity processes affecting melanin pigmentation[22]. These properties not only provide promising alternatives for the management of hyperpigmentation but also facilitate more synergistic and multifaceted treatment[23]. However, nano emulsions lack intrinsic medicinal activity and the use of only metallic NPs, either isolated or incorporated in solid carrier matrices, have certain challenges such as poor dispersion, potential aggregation, uncontrolled release of NPs, limited epidermal persistence, as well as possibility of cytotoxicity in higher doses[24]. To combine the desirable characteristics of nano emulsions (i.e. Excellent solubility and bio-availability and high skin penetration capacity) with the potent therapeutic efficacy of metallic NPs, hybrid platforms have been designed[25]. A recent research approach demonstrated effective formulation of hybrid nano emulsion-metal NPs system in which metallic nanoparticles are dispersed within oil droplet of an nano emulsion[26]. These formulation strategy demonstrate advantages over each component system separately, namely, improved dispersed state of NPs, enhanced formulation stability and stability during skin application, extended drug permeability across to skin, and prolonged accumulation of the NPs to specific skin site (such as Melanocytes) and more importantly, combined effect to simultaneously overcome the effect of ROS, chronic inflammation, melanogenesis, melanosome transfer and UV-induced epidermal damage of skin by the active metal NPs[27]. Although there has been a major advances in the understanding of each nano carrier systems respectively and a few studies on combination strategy, a comprehensively integrated review discussing on combined molecular mechanism behind of hyperpigmentation and recent therapeutic approaches focused to nano emulsion systems, metal nanoparticles and nano emulsion-metal nanoparticles hybrids will be benefit to researchers and clinics working on the field[28]. The focus herein will be on bringing forth comprehensive discussion of underlying hyperpigmentation mechanisms, and on highlighting of potential nanotechnological applications in treatment such as nano emulsions alone and combined with metal nanoparticles that offers new promising approaches for hyperpigmentation[29]. The article aims to address deficiency in the scientific literature by bridging understanding on molecule dynamics, recent nanotechnological developments on innovative solutions, artificial intelligence assisted nano delivery systems, 3D human skin models, and the future challenges of commercial application of those strategies to develop advanced and reliable nanotherapeutics for treating pigmentary disorders[30].

2. MOLECULAR BASIS OF HYPERPIGMENTATION

2.1 Skin Pigmentation Biology

The skin color is regulated genetically and the other genes contribute to the melanin production responsible for darkening the skin[31] . Skin pigmentation is regulated biologically but it's also influenced by environment factors. Melanocytes Melanosomes Keratinocytes Skin pigmentation regulation mediated by complex interplay of cells melanin pigments are produced by melanocytes, melanomas are involved in carrying these melanin pigments while Keratinocytes protect from them[32]. The epidermal melanin unit, consists of melanocytes , melanosomes and keratinocytes cooperatively responsible for this pigment process[33]. An imbalance in this cascade or abnormal activity can contribute to

hyperpigmentation and skin darkening conditions like post inflammatory hyper pigmentation (PIH), melasma, solar lentigines etc. [34]. The functions performed by each of them can be explained as: 1. Melanocytes It is a kind of dendrite cells found mostly on basal layer of both Epidermis and the hair follicles[35]. Melanocyte counts only for 5 to10% of the epidermal cells yet all these 10% alone are responsible for production of melanin[36]. They are affected by UVB radiation, oxidant stress, hormone signaling, inflammatory media and increase melanin synthesis accordingly[37]. In response of UV radiation, they elongate to reach out the neighboring skin cells and deliver the pigments in to them[38]. Other than pigmentation, these cells play role in photoprotection reducing UV mediated DNA damages [39]. The melanocytes respond and alter their functions when expose to environmental stimulus. Melanosome These are special type lysosome-related organelles unique to the melanocyte cells. These vesicles perform storage and carry melanite in them[40]. There are 4 stages of their maturation process (melanosome stage I, II, III, IV from immature and empty to complete melanosome fully colored[41]. These mature melanosomes contain either the (eumelanin or pheomelanin) pigments that are distributed in the adjacent keratinocytes[42]. The process of transport happens via motor proteins. Proper maintenance of maturation and delivery process is required for even skin coloring the malfunctioning or defects can lead to severe pigmentary problems. 3. Keratinocytes These are epidermal skin cells that compromise almost 95% of epidermal area but still active regulation of Skin Coloring is by melanocytes[43]. Though, upon stimulus with UVB radiation these skin cells secret certain growth factors like stem cell factor (SFC), -melanocyte-stimulating hormone (-MSH) and endothelin-1that encourage the melanocyte to produce melanin[44]. The melanocytes produce the matured melanosome which is transferred to keratinocytes. Here the delivered melanosome is placed above nucleus to shield DNA. Other ways of regulation involve skin turnover and degradation of some to predict overall skin shading intensity and persistence of skin color[45]. Skin pigmentation regulation is regulated by these skin color regulating elements of melanocytes, melanosomes and Keratinocytes, in a way where defects occur in the proper process of any of these element results into skin pigmentation like hypopigmentation and hyperpigmentation and their therapeutic management using Nano carriers system is of huge concern at present for their efficacy in delivering active principles in regulated manner for treatment of these type of disorders[46,47].

2.2 Molecular Regulation of Melanogenesis

Melanogenesis The biological processes that govern melanin production in melanocytes Melanogenesis is a highly regulated multistep cascade that generates pigmentation and is dictated by precise control of enzyme activity, transcription factors, intracellular signals and cell surface receptors which collectively control production and the quality of melanin pigments in cells[48]. In response to environmental and biological stimuli such as uv-radiation, oxidative stresses, hormonal factors and inflammation, the complex melanogenesis related pathways in melanocytes contribute to the proper equilibrium of skin pigmentation, which would otherwise become over active and causes hyperpigmentation conditions[49]. Type and amount of melanin The most important enzyme for this series is the rate-limiting enzyme tyrosine. The first two steps involved tyrosinase which convert L-tyrosine into L-DOPA, which is in turn further conversion to dopaquinone by tyrosine in order to form melanin pigments. After activation of tyrosine and subsequent dopaquinone formation[50]. Tyrosinase related protein 1(TRP-1) and Tyrosinase related protein 2 (TRP-2, also called as dopa-quinone-transaminase, DCT) involved in later stages to facilitate several downstream steps for either production or improvement on storage, or enhancement on defense against oxidative stress to maintain the concentration or quality of melanin or. Increase expression of try, TRP-1,TRP-2 are tightly correlate with the elevated level of melanin[51]. The central regulator for expression of tyranny, TRP-1, TRP-2. Melanogenesis is a very tightly controlled process and the transcription process is mediated largely by the microphthalmia-associated transcription factor (MITF)[52]. Microphthalmia-associated transcription factor (MITF) MITF as the master regulator of pigment and differentiation plays a significant role to control entire melanogenesis. MITF regulate overall expression of the tyrosinase related families' members[53]. Thus, to make the regulation of abnormal pigmentation, targeting MITF would be one strategy and MITF gene expression is controlled by the convergence of numerous signaling pathways[54]. The melanocortin 1 receptor(MC1R). Upon UV-induced signals, keratinocytes release proopiomelanocortin (POMC) that gets converted to -melanocyte-stimulating hormone (-MSH). Binding of -MSH with its cognate receptor, MC1R, which present in melanocytes cell surface ,(a G-protein coupled

receptor) triggers the activation of adenylate cyclase leading to generation of intracellular camp which in turn actives pka, phosphorylation of CREB and induction of MITF mRNA expression thus leads to stimulation of pigmentation processes with generation of tyrosinase, TRP1 and TRP2 genes[55,56].MC1R/cAMP/CREB/MITF axis is the most principal pathway regulating melanin synthesis and plays central role in pigment formation, It is of paramount Importance for both the determination of UV response and skin tone, so this signaling system is considered as the main targets of pigmentation therapeutic drugs and many others signaling regulators that affects activation/inhibition of the signals for melanin biosynthesis (Fig)[57]. Other pathways involving: mitogen-activated protein kinase (MAPK) pathway. Activation of ERK in particular negatively regulates MITF stability, thus decreases melanogenesis. Conversely, activation of p38MAPK enhances MITF levels and promotes pigment production , especially upon UV stimulation .it seems that selective inhibition of the MAPK axis would potentially be effective in ameliorating unwanted hyperpigmentation[58]. Furthermore Went/-catenin pathway, one of key regulation pathway not just for Melanocyte DEVELOPMENT and survivals, but for the establishment of epidermal melanin unit through stimulating MITF gene expression[59]. want signaling activation leads to accumulation of-catenin in the cytoplasm that enters the cell nucleus and binds with transcription factors to up-regulate MITF expression and consequently stimulate the expression of melanogenic enzymes leading to pigment production[60]. Activation and hyperactivation of Wnt/catenin signaling pathway are known as causative factors for various types of skin hyperpigmentation's, therefore, Want signaling pathway could also be a potent therapeutic target.[61] In summation. All in all, the entire signaling networks in melanocytes integrate to intricately regulate melanin synthesis to a state of delicate physiological equilibrium[62]. Overactivation of tyrosinase-MITF signaling pathway results in excessive accumulation of melanin causing hyperpigmentation condition and many studies now focused on developing targeted remedies that disrupt specific molecules in this signaling network[63]. With advance in formulation of innovative nanocarriers systems enabling the highly efficient delivery of Melanogenesis inhibitors to melanocyte, the treatment efficacy and off-target effects would considerably improve[64].

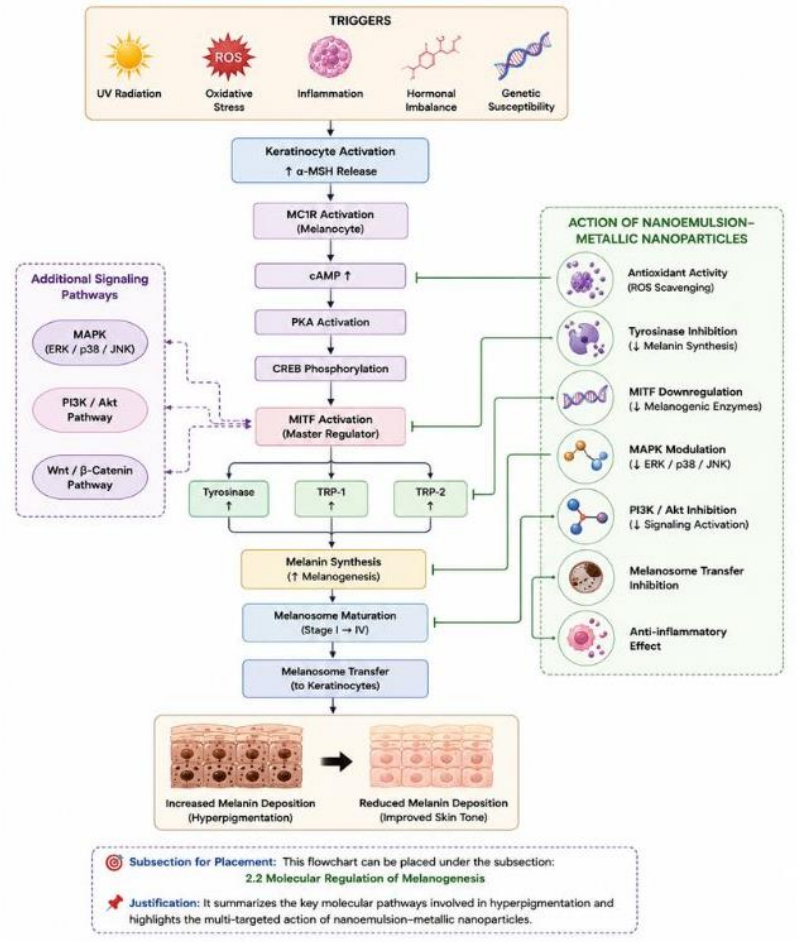


Figure 1. Molecular regulation of melanogenesis and modulatory effects of nano emulsion–metallic nanoparticle systems. Created with BioRender.com.

2.3 Oxidative Stress and Hyperpigmentation

When our skin encounters environmental and lifestyle factors, the antioxidant balance in the skin becomes overwhelmed [65]. As your skin is pushed, the bad guys in the skin, known as free radicals, proliferate or become overabundant, with an increase in reactive oxygen species that overstimulate the skin pigment factories, melanocyte cells, causing hyperpigmentation[66]. Chronic exposure to environmental stress factors or even simple daily UV or sun exposure stimulates melanocyte cells to hyperproduce melanin, resulting in what we know as skin pigmentation, which in turn stimulates chronic pigmentary disorders[67]. Our melanocytes cells are triggered by information, which at some point when overstimulated by ROS will cause activation and subsequent process of pigment[68]. So basically, you get into and endless cycle of stress, inflammation and eventually pigmentation, which becomes activated by even normal skin functioning signals as the process can be sustained or self-reinforcing with further information from signals that are received that perpetuates skin cells into and overactive production[69]. Free radicals essentially "attack" damaging proteins, lipids & amino acids leading to Premature aging. In pigment-producing skin cells the bad Guys actually have a way of making their own melanin on Steroids! For anyone with hyperpigmentation problems such as melasma, PIH, you most certainly Recognize the signals in how the trigger that feeds the fire of problem on an endless loop! [70]We produces inflammatory responses via cytokines signals to keep signaling or sending more signals that in return will continue to induce a particular behavior of other signals, leading to further inflammatory process and in tern leads to the over-production of pigment in an endless cycle! When speaking about melanocyte functions all roads in an signal pathways led to a very significant

Transcription Factor that directs pigments, called MITF, the chief officer of melanocytes as it is referred to, processing the signals it Receives from either within or externally to make our skin colored pigments[71]. Through this mechanism, all the players (oxidative stress or Bad Guys/ Inflammation (a byproduct that is part of the over-production and signals of bad guys / AND MITF, the 'control central'), combine to make the perfect storm for a sustained overproduction of color (aka pigment)! This becomes the " Chronic pigmentary disorders[72]." And is precisely Why these conditions RESIST most forms of treatment and it may appear to seem impossible to get your clear complexion, because you keep running through the triggers and a chronic cycle that continues to feed and exacerbate your condition[73].

2.4 Melanosome Biogenesis

Melanosome biogenesis is a carefully managed process inside cells that controls how melanin-filled structures are made get ready move around and get passed from melanocytes to keratinocytes[74]. This process is very important for deciding how dark the skin is and keeping it safe from the sun's rays. In addition to making melanin controlling how melanosomes move has become very important in causing problems with much pigment[75]. This has made it a good focus for treatments that try to reduce pigment. Melanosomes start from the -lysosomal system and go through four steps to get ready. Step one melanosomes are round and not yet ready[76]. They have some parts but no color. In step two a special protein called PMEL makes a shape that helps color get put in. At this point the structures are not colored yet. Can get the tools needed for making color. In step three the tools needed for making color get brought in. This starts the process of making melanin. In step four the structures are completely ready and full of color[77]. They are the working pieces that get moved around inside the cell. After they are ready the melanosomes move from the middle of the melanocyte to the ends of the branches[78]. This moving is along microtubules over long distances and other strands called actin filaments for very short distances. Proteins in the cells like Rab27A, MLPH, and myosin Va help this happen[79]. It makes very sure, to make, and keep pigment, in the correct location and on The last portion is When the melanosomes, prepared To deliver their melanin pigment, begin to emigrate (move) from melanocytes to epidermal keratinocytes[80]. This cell dispersal mechanism can occur by means of exocytosis of macrovesicles or macrovesicles, melanosome-keratinocyte fusion, or transfer through intercellular nanotubes; in addition, keratinocytes possess active up take of melanosomes, especially from above[81]. Upon uptake into keratinocytes, melanosomes is delivered on top of nuclear layer The melanosomes will line themselves at the uppermost surface of keratinocyte nuclei to cover DNA cells (provide a protective umbrella-like screen effect against ultraviolet)[82]. The number of melanosomes per cell, size distribution, breakdown time and time of skin rejuvenation all are the decisive factor of skin pigmentation level. Disorders in any step on synthesis and transport, and distribution within cell of melanosomes will bring about excessive color even under norm melanocytes amount[83]. Newly strategies aim at to either controlling the function of melanosomes or blocking melanin production directly. For example, new vehicle delivery technologies, including nano emulsions [50] are investigated. Nano emulsion technology can deliver actives which can inhibits melanosomes growth and transfer and lightens skin safely[84].

3. CONVENTIONAL TREATMENT STRATEGIES

The main goal of treating hyperpigmentation is to reduce the amount of melanin in the skin help the skin turn over faster and stop the hyperpigmentation from coming. Doctors usually treat hyperpigmentation with creams, pills and special procedures[85]. These methods are commonly used. They can be limited because they do not work well for everyone can irritate the skin and may not work for a long time. Creams that reduce pigmentation are usually the choice for treating hyperpigmentation[86]. Hydroquinone is a medicine for this because it stops the skin from making too much melanin. However, using it for a time can cause skin irritation and other problems. There are common creams used to treat hyperpigmentation, such as kojic acid, azelaic acid, arbutin, niacinamide, vitamin C, retinoids and tranexamic acid[87]. Each of these creams works in a way to reduce melanin in the skin. Doctors often use a combination of creams to get results and minimize side effects. Some people also take pills, like acid and antioxidants to treat hyperpigmentation that does not respond to treatments[88]. These pills help by reducing inflammation and stress in the skin.. They need to be used carefully because they can have side effects. There are also procedures like chemical peels, laser therapy pulsed light and microneedling that can help reduce hyperpigmentation[89]. These procedures can work quickly. They can also cause side effects like more

hyperpigmentation, redness and are often expensive especially for people with darker skin[90].With all these treatment options there is no treatment that can completely cure hyperpigmentation. The creams and pills do not always work well. The procedures can be expensive and have side effects[91]. This is why scientists are working on ways to deliver medicine to the skin using particles called nanotechnology. These particles can help the medicine work better longer. Cause fewer side effects. This new technology has the potential to overcome many of the problems with treatments for hyperpigmentation[92].Hyperpigmentation is a problem that affects people and finding a good treatment for hyperpigmentation is an important goal, for doctors and scientists. They are still looking for better ways to treat hyperpigmentation[93]. Hyperpigmentation treatments are still being. New discoveries are being made to help people with hyperpigmentation[94].

4.1 NANO EMULSION FUNDAMENTALS

Nano emulsions is a drug that delivers the active in to the body. Nano emulsions consist of oil and water that would not mix properly, but they become stabilizes using agents that are generally termed as emulsion helpers called emulsifiers or surfactants[95] . Nano emulsions are small size (Typically ranges 20 – 200 nm) that make them suitable for the use as they exhibit both good stability and can deliver drugs to the body successfully. There are about two major classifications which Nano emulsions fall under, namely oil – in – water nano emulsions and water – in – oil nano emulsions, with the former been broadly useful in the skin condition based on its oil-free property making it ideal for most individuals[96]. They, due to their small size can closely fit together so effectively that the enhanced and effective drug penetration happens in compare to conventional topicals which are topical treatments applied to the skin. It assists the drugs to keep suspend in between the skin therefore making the drugs preventing their permeation into another segment of body[97]. A typical nano emulsion system involves typically four distinct basic ingredients, and which we have meticulously formulated to enhance on the effective functioning of the Nano emulsion which contains, The Oil(drug carries), an Aqueous Phase(watery surround layer),Surfactant(an emulsion help, mixes and stabilizes oil and water),Co Surfactant(an emulsion mixture stabilizer). Nano emulsions are super for effective penetration better that traditional creams and gels and have considerably less skin inflammation. Nano emulsions perform best when introducing Drugs which are often difficult penetration the skin[98] .we can successfully introduce this Drug store make them work in the skin efficiently ,we cane help a people with skin related problem like hyper pigmentation by sending drug the proper site thus enabling good results and to helping a man in Reducing Inflammation and oxidizing stress contributing to numerous skin disorder [99].hence nano emulsions has efficient method of delivery of Drugs- to the body and is very well use, it easy of Application , Quick absorption in the skin, minimal risk of skin irritation, better penetration into the skin for better use, good for treating multiple problem. Nano emulsion system has proved to be efficient route in sending Drugs an overall good stability, minute size and capacity to effectively penetrate skin and therefore has been very widely used for the successful management of inflammatory skin conditions and problem like skin hyper pigmentation and stress in the skin which nano emulsions can effectively heal and treat, thus nano emulsion is a beneficial option for Skin Disorders[100].

4.2 PREPARATION METHODS OF NANO EMULSIONS

The way we make nano emulsions is very important. It affects what they are like and how well they work. We can make nano emulsions in two ways: using a lot of energy or not much energy[101]. The way we choose depends on things like what's in the nano emulsion and what we want to use it for.When we use a lot of energy we can make the droplets of nano emulsion small. This makes them work better[102]. One way to do this is with high-pressure homogenization. We force the mixture through a hole at very high pressure. This makes the droplets very small. It is a way to make a lot of nano emulsion. We can also use waves to make the droplets small[103]. This is called ultrasonication. It is simple. Does not cost much. It is good for making amounts of nano emulsion. Another way is to make two streams of crash into each other at high speed. This makes the droplets very uniform and stable. Using a lot of energy has some problems. It needs equipment and uses a lot of power. It might not be good for some medicines that're sensitive to heat[104].On the hand we can make nano emulsions with not much energy. We use the properties of the mixture to make the droplets small. This way is good for medicines that're sensitive to heat. One way to do this is to change the temperature of the mixture[105]. This is called the Phase Inversion Temperature method. When the temperature is just

right the mixture forms small droplets easily. We can also change the recipe of the mixture to make it form droplets. This is called the Phase Inversion Composition method. Another way is to mix the oil and water gently. The oil will form droplets by itself. This is called emulsification It is a way to make nano emulsions[106].The way we make nano emulsions is important. If we want to make a lot of nano emulsion and have control over the size of the droplets we should use a lot of energy. If we are working with medicines that are sensitive to heat we should use less energy. We need to choose the way to make the nano emulsion so that it works well and is safe to use[107].For example when we are making a treatment for hyperpigmentation, we need to choose the way to make the nano emulsion. We want it to work well and be safe for the skin. So we need to think about what's in the nano emulsion and how we are going to make it[108]. This way we can make a nano emulsion that's stable and works well. Nano emulsions are very useful for treating skin problems, like hyperpigmentation. They can help the medicine get into the skin better and work effectively[109].We need to make them in the right way so that they are safe and effective. In conclusion making nano emulsions is a process. We need to think about what we're using them for and how we are going to make them[110]. We can use a lot of energy or not much energy. Both ways have advantages and disadvantages. We need to choose the way to make the nano emulsion so that it works well and is safe to use[111].The way we make nano emulsions is important. If we want to make a lot of nano emulsion and have control over the size of the droplets we should use a lot of energy. If we are working with medicines that are sensitive to heat we should use less energy[112]. We need to choose the way to make the nano emulsion so that it works well and is safe to use. For example, when we are making a treatment for hyperpigmentation, we need to choose the way to make the nano emulsion. We want it to work well and be safe for the skin. So we need to think about what's in the nano emulsion and how we are going to make it[113]. This way we can make a nano emulsion that's stable and works well. Nano emulsions are very useful for treating skin problems, like hyperpigmentation. They can help the medicine get into the skin better and work effectively. We need to make them in the right way so that they are safe and effective[114].In conclusion making nano emulsions is a process. We need to think about what we're using them for and how we are going to make them. We can use a lot of energy or not much energy. Both ways have advantages and disadvantages. We need to choose the way to make the nano emulsion so that it works well and is safe to use[115].

4.3 ADVANTAGES OF NANO EMULSIONS OVER CONVENTIONAL FORMULATIONS

Nano emulsions really help your skin when used as a delivering skin medicine in cream and gel they are just as powerful but since they are 20-200 nanometers then the amount of the drug is more effective when used by you, they also help in receiving more amounts and so the results would be much efficient[116]. The skin products have surface area so help is received with efficiency they are not harmful as you can take you medication while they are in your delivery or on your face it should be kept aside and your medicine would do their work well, and cannot be separated or altered in size and shape over the period of time[117].With some helpers called co and surfactants to make everything in it uniform the medicine should not spoil when exposed to any conditions hence they are kept in condition by nano emulsions you may get you skin discoloration in it they shall be useful they shall transfer medications which may help in skin discoloration to some and stop the mechanism by destroying those agents the user of the products may not apply cream and gels again and again with no burning sensation in particular are good skin feelers, and would always lead you to utilize as per recommendation[118].Success of nano emulsions in treatments is mainly due to their capability in passing across skin barrier to act on targeted site. The outer most layer is defined as Stratum Corneum, the skin's outermost protection barrier with highly organized and closely packed lipid structures, impedes drug penetration, therefore hindering effective delivery to desired stratum cells and causes low bioavailability by current skin application methods. Whereas nano emulsion tiny size and huge surface area in optimum lipid constitution allows better penetration. When applying, its minute sized oil droplets engage with lipids layer of the skin cells[119]. Their specialized help of surfactants and co-surfactants helps to temporarily loosen skin lipids structure that facilitates easier penetration of medication within skin cell through various paths between the cell, along the skin cell as well as through pores, hair and sweat glands, in order to gain penetration to the target location, without serious or substantial damage. Once the formulation crosses the stratum corneum barrier it diffuses down into the cell layer of the skin which is involved with production of melamine (MEL)[120]. Because of its improved facility to achieve the targeted cells directly it can efficiently block pigment (melamine)

producing agents like Tyrosinase & MITF, thus controlling MEL production which would lead to a successful therapeutic outcome for the treated area[121]. Additionally, these nano emulsions deliver active compound to skin in a sustained controlled release fashion and persist in skin for a considerably long period of time thus reduce the frequency of application and minimizes local irritating properties of the drugs. Better permeability due to nano emulsions technology allows successful delivery of phytochemical, antioxidants and skin depigmenting agents while maintaining stability & higher bioavailability of actives, hence; based products based on nano emulsions can be used for controlling pigmentation because it provides topical drug delivery at targeting cell(s) only without systemic distribution causing side effects[122].

5. METALLIC NANOPARTICLES FOR HYPERPIGMENTATION THERAPY

Metallic nanoparticles, which are of many uses in skin care due to the properties it carries. The property includes their vast surface area, their size can be tailored and we can modify the surface to keep it stable. Some other agents can be attached to their surface. Unlike agents used for making skin color lighter, the metallic nanoparticles are not just useful for delivery of drug, it has some other abilities as that of halting oxidation and inflammation[123]. It fights germ and makes skin color healthy. There are several types of metallic nanoparticles which can be useful in treatment of skin color. Namely silver, gold, zinc oxide, titanium dioxide, iron oxide and copper oxide nanoparticles, each of them has their unique method of acting and are used to achieve distinct purpose in skin disorders. Silver and gold nanoparticles are common agent because, it is found that these particles inhibit excessive color generation in skin by reducing oxidation and making alteration in the mechanism of color generation by skin. Zinc oxide and titanium dioxide are used as major constituent in sunscreens because they block sunrays to damaging it and makes excessive color not generated[124]. Iron oxide particles possess ability of being useful for drug delivery to respective location as well as for skin imaging. Copper oxide nanoparticles are very useful in skin disorders. They attack microbes and also play a role in altering skin color[125]. Although different metal nanoparticles act differently in treatment they all possess the common aim of altering skin color either by decreasing the formation of color by skin cells or reducing stress developed by sunlight over skin. With the advantageous aspects of metallic nanoparticles, we should always be cautious of how much we are using, what their size is, whether it is non-toxic and does it have harmful long-term effect over skin[126]. Presently various researches are in phase to encapsulate the nanoparticles within systems which can allow easier transport over and through skin, reducing the bad effect and carrying the agent to the desired location. The advancement of metal nanoparticles utilization in skin problem is another step ahead to manage color related disease in skin. Hence metallic nanoparticles are also a choice for skin color modification therapy[127].Silver nanoparticles (AgNPs) are of significant interest among skin researchers because of the properties they possess. First, AgNPs can readily interact with the human body and their increased surface area allows for the effective treatment against negative substances (e.g., bacteria). In addition, silver nanoparticles have some useful characteristics that can potentially benefit the skin's health. The latter has recently allowed us to investigate the application of AgNPs in the treatment of hyperpigmentation, which is over pigmentation of the skin. Silver nanoparticles are able to deliver some compounds that lighten the darkened spots in addition to having other mechanisms to reduce pigment production. Silver nanoparticles are beneficial in hyperpigmentation treatment as they can inhibit tyrosinase, an enzyme that is responsible for melanin production[128]. Silver nanoparticles also reduce reactive oxygen species (ROS), a compound that promotes hyperpigmentation. Some research suggest that silver nanoparticles also reduce the amount of MITF (a protein that plays a critical role in melanin production) thereby reducing hyperpigmentation. Silver nanoparticles also help reduce inflammation that cause redness and irritation. This benefits individuals suffering with inflammatory hyperpigmentation (PIH). Additionally, we can design nano emulsions and hydrogels containing the silver nanoparticles in a localized delivery system that increases retention and penetration of silver nanoparticles in skin, maximizing its benefits, and at the same time preventing it from circulating in the body and increasing the likelihood of a negative outcome. We can even develop AgNPs from plant extracts and increase its biocompatibility and provide additional beneficial properties. Studies show that AgNPs have the ability to reduce melanin production and inhibit its activating enzymes[129]. Some studies indicate that although data is limited it seems that AgNPs are capable of providing good and safe treatments without any side effects, however much more studies have to be performed to verify their safety and dosage in various types of

hyperpigmentation treatment. Silver nanoparticles show great potential as treatments in hyperpigmentation. We are excited to know the outcomes of future study. We will continue our research and to know how they may help people suffering with hyperpigmentation[130].

5.1 SILVER NANOPARTICLES (AGNPS)

5.2 ZINC OXIDE NANOPARTICLES (ZNO NPS)

Zinc oxide nanoparticles are widely used in dermatology because they have ability to block UV light. They are safe for the body. Have good antioxidant and anti-inflammatory effects. Because they are so small zinc oxide nanoparticles offer protection against both UVA and UVB rays. They also look good on the skin. Since ultraviolet light is a cause of more pigment being made zinc oxide nanoparticles help in stopping and controlling skin conditions that cause too much color, like melasma, post-inflammatory hyperpigmentation and solar lentigines[131]. The way zinc oxide nanoparticles help with much color is not direct. They. Scatter UV light. This stops skin cells from getting activated. This lowers the release of things that make pigment, like alpha-melanocyte-stimulating hormone and inflammatory chemicals. This also stops a pathway from working which causes less of the enzymes that make melanin. In addition, zinc oxide nanoparticles help by removing molecules called reactive oxygen species. This reduces the amount of pigment caused by stress. Another good thing about zinc oxide nanoparticles is that they reduce inflammation. They lower the amount of chemicals and help the skin get better[132]. This makes them helpful for skin problems that cause lasting color changes. Also zinc is important for healing skin and fixing areas. This helps the skin get better and lowers the chance of pigment. Zinc oxide nanoparticles are added to things like nano emulsions, creams, gels and sunscreens. This makes them better at staying on the skin and working well. Formulations with nano emulsions help spread the nanoparticles and make them work better[133]. They also help avoid the look that regular zinc oxide can have. These advanced ways of putting the nanoparticles on the skin also let other helpful things be added together. This gives results. Many studies have shown that zinc oxide nanoparticles are safe and work well when used in the amounts. They do not break down under sunlight. Do not go deep into the skin. This makes them safe. They are one of the accepted materials, in the beauty and medicine industries. Overall zinc oxide nanoparticles help with much pigment by offering UV protection removing harmful molecules reducing inflammation and making it easier to apply on the skin. This stops the skin from making much color and helps keep the skin color normal over time[134].

5.3 EMERGING NANOPARTICLES FOR HYPERPIGMENTATION THERAPY

The new ways of hyperpigmentation treatment are very advanced due to the developments in nanotechnology. The methods no longer just use metal nanoparticle. We have new types of materials to create nanoparticles including, cerium, oxide, selenium, copper, silica and special hybrid nanoparticles. These new nanoparticles come with a combination of useful characteristic such as: inhibiting radicals, delivering drug to a targeted site and releasing drugs slowly and are able to be safely applied to the body[135]. The new type of nanoparticles have allowed to target melanin production in cells and to have less dangerous side effects compared to what existed previously. Some nanoparticles like that of cerium oxide have amazing anti-radical capabilities; this occurs because the atoms can turn between two states allowing them to purify the toxic free radicals in the skin, reducing skin inflammation and slowing melanin production. Another anti-radical agent is selenium particles; these nanoparticles reduce inflammation and protect Melan producing skin cell from being harmed and prevent formation of melanin produced compounds. The are also safe and non-toxic and are used to delivery drugs in a timed matter to the target region of skin; however their use against hyperpigmentation needs further investigation. Copper and copper oxide nanoparticles have a lot of amazing properties such as: inhibiting the growth of adverse bacteria's in skin, suppressing radicals damage, regulating enzyme production and more[136]. Copper is an essential element in skin and these nanoparticles may regulate multiproduction in the skin, reduce inflammation and help the skin heal. Although copper is known for treating hyperpigmentation, further study is needed to learn how to effectively use nanoparticles of copper. Due to the high surface area of the nanoparticles and their ability to deliver drugs in timed delivery, we can used them to create drugs which, combined with many antioxidants , natural extracts, can penetrate deeper in to the skin to maintain healthy and lasting effects and extend drug action to a sustained release time in the skin[137]. The nanoparticles hybrid nanoparticles combine the high performing and effective benefits of metal nanoparticles with the enhanced delivery properties and safety of polymer nanoparticle technology; such

nanotechnology allows to carry several effective drugs in an array and together; they not only act on fighting radical' damage but also on reduction of inflammation. And also targeting melanin producing cells as mentioned for other forms. We also can produce a broad spectrum of this nanotechnology that enables to overcome skin barrier to target deep issues such as melasma[138].

Table 1. Metallic nanoparticles for hyperpigmentation therapy

Nanoparticle	Principal mechanism	Major therapeutic role	Evidence status	Key limitation
Silver nanoparticles (AgNPs)	Tyrosinase inhibition; ROS modulation; MITF-associated regulation	Suppression of melanogenesis; antioxidant and anti-inflammatory activity	Preclinical/experimental	Dose-dependent cytotoxicity; limited clinical evidence
Gold nanoparticles (AuNPs)	Modulation of melanogenic signaling; antioxidant activity	Regulation of melanin synthesis and inflammatory responses	Experimental	High cost; limited hyperpigmentation-specific evidence
Zinc oxide nanoparticles (ZnO NPs)	UVA/UVB attenuation; ROS reduction; anti-inflammatory effects	Photoprotection and prevention of UV-induced pigmentation	Established topical use/emerging therapeutic application	Need optimization of particle size and formulation
Titanium dioxide nanoparticles (TiO_2 NPs)	Physical UV scattering and absorption	Photoprotection and reduction of UV-triggered melanogenesis	Established topical use	Limited direct melanogenic activity
Cerium oxide nanoparticles (CeO_2 NPs)	Redox activity and ROS scavenging	Reduction of oxidative stress and inflammation associated with pigmentation	Emerging	Limited long-term dermal and clinical data
Selenium nanoparticles (SeNPs)	Antioxidant and cytoprotective activity	Protection against oxidative stress and inflammatory pigmentation	Emerging	Safety and dose optimization required
Copper/copper oxide nanoparticles (Cu/CuO NPs)	Antioxidant, antimicrobial and inflammatory pathway modulation	Potential regulation of pigmentation and skin repair	Emerging	Concentration-dependent toxicity; limited clinical evidence
Polymeric–metal hybrid nanoparticles	Combined delivery and multifunctional biological activity	Targeted, sustained and multimodal pigmentation control	Emerging	Complex formulation and scale-up

6. MOLECULAR MECHANISMS OF METALLIC NANOPARTICLES IN HYPERPIGMENTATION THERAPY

Metallic nanoparticles play role in improving dark spots, and uneven skin tone. The method of which it works isn't one singular mechanism. Its efficacy lies in the fact that it can target numerous things at one time. These few things includes; enzymes that produce melanin signals, oxygen in cells, inflammation of the skin, and the transport of melanin. This mechanism of working isn't found in any of the other dark spot remedies. Metallic nanoparticles are starting to become popular as good treatments for various types of skin pigmentation problems. Tyrosinase Inhibition: Tyrosinase is an enzyme necessary in the process of producing melanin, by acting to convert tyrosine to L-DOPA to dopaquinones[139]. Silver and Gold nanoparticles are potent blockers of this enzyme; it can achieve this by directly associating with the enzyme or by reducing the amount present. The inhibition of this enzyme plays a role in the reduction of melanin producing factors. MITF Regulation: Microphthalmia-associated transcription factor, otherwise known as MITF, controls melanin production in skin cells. It regulates tyrosinase, TRP-1 and TRP-2 synthesis. Metallic nanoparticles can act to prevent the signal pathways preceding MITF therefore not allowing the genes responsible for melanin production to be produced. Suppressing MITF will lead to a halt in melanin synthesis and activity of melanocytes[140]. This has a therapeutic potential in the treatment of hyperpigmentation. ROS Scavenging: The stress placed upon skin cells from reactive oxygen species (ROS) can contribute to increased melanin production. Cerium oxide nanoparticles, as well as selenium, and gold, are effective in reducing the stress on cells and are therefore responsible for decreasing the quantity of melanin produced. UV Protection: Zinc oxide and titanium dioxide nanoparticles block solar radiation. By scattering solar rays the cells prevent their production of melanin thus halting the creation of dark spots. Inflammatory Action: Increased inflammation in skin tissue can contribute to exacerbation of dark spots and the increase of their size. This aspect is diminished by metallic nanoparticles which decrease chemical mediators and internal cellular stress making conditions favorable to melanocytes, thus slowing the production of melanin, further ameliorating dark spots. Overall, it can be seen that metallic nanoparticles work on numerous steps in the cascade of melanin production including; the enzymes that promote it, factors in the production of the aforementioned enzymes, stresses acting upon the cells, moving of melanin, and blocking solar radiation. This multifocal approach by metallic nanoparticles makes it an ideal treatment for dark spots[141,142].

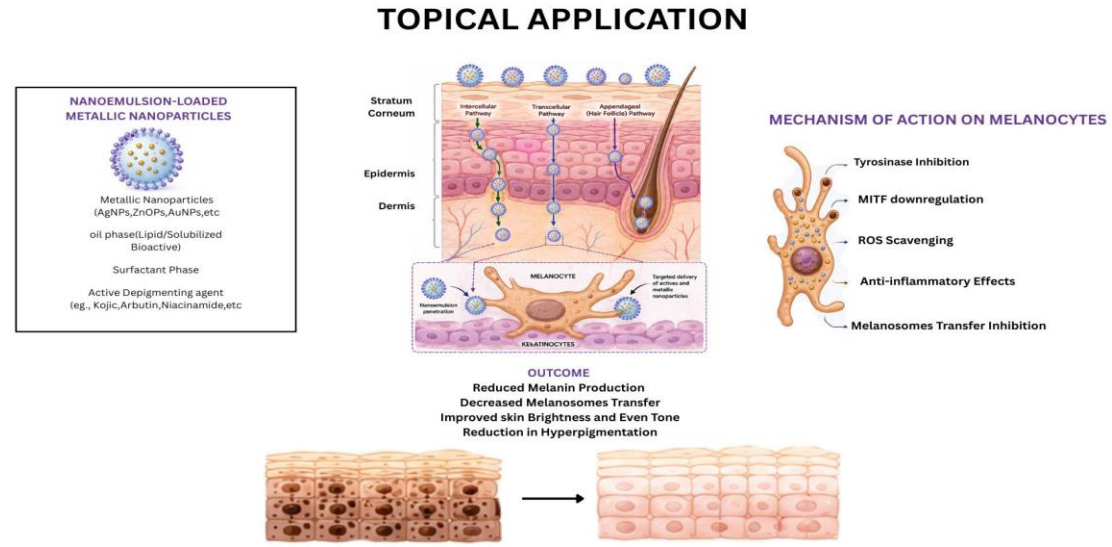


Figure 2. Multifaceted molecular mechanisms of metallic nanoparticles in hyperpigmentation therapy. Created with BioRender.com.

7.HYBRID NANOEMULSION–METALLIC NANOPARTICLE SYSTEMS: A NOVEL STRATEGY FOR HYPERPIGMENTATION THERAPY

Nanoparticles paired with nano emulsion-based delivery systems are a novel and promising approach to tackling hyperpigmentation. Metallic nanoparticles carry valuable traits that support the halt of melanogenesis, which is primarily responsible for the production of hyperpigmentation and their antioxidant and anti-inflammatory properties. Although beneficial, their dispersion is limited, and high concentrations are not conducive; conversely, nano emulsions excel in drug penetration into the skin and sustained release without their inherent biological attributes. Combining the two technologies therefore merges the advantages of both[143].The synergy between nanoparticles and nano emulsions lies in their complementary nature. Metallic nanoparticles such as silver, gold, zinc oxide and cerium oxide are known to inhibit melanin genesis by suppressing tyrosinase, the culprit behind hyperpigmentation. Furthermore, these particles boast antioxidant and anti-inflammatory benefits. Delivering these nanoparticles to the deepest layers of the skin where melanogenesis occurs -the basal layer of the epidermis - is a challenge, but nano emulsions enhance this delivery by increasing their skin penetration. A remarkable aspect of incorporating metallic nanoparticles into nano emulsion-based systems is enhanced penetration into the skin. The microscopic lipid droplets that comprise nano emulsions readily interact with the skin's outermost barrier, facilitating nanoparticles to permeate deeper[144]. This increases the proportion of active ingredients reaching their target site, maximizing their effectiveness. Another significant advantage is the sustained release profile that these hybrid systems offer. Nano emulsion droplets act as mini repositories, gradually releasing nanoparticles and other active components over time. This ensures a continuous supply of therapeutic agents to the skin, improving efficacy and reducing the need for frequent application. Additionally, the hybrid systems demonstrate greater stability than individual nanoparticles, which are prone to aggregation and potential loss of biological activity over time. When enshrouded within nano emulsion droplets, these nanoparticles are shielded from degradation, prolonging their potency-a promising stride in the treatment of hyperpigmentation. Metallic nanoparticles and nano emulsions function as a well-coordinated team in addressing hyperpigmentation; the former interrupts the color production cycle, while the latter ensures they reach their destination. Combining these technologies can result in a more efficacious treatment with a lower potential for side effects, marking an exciting avenue of research poised to improve hyperpigmentation management strategies[145].The use of nanoparticles within nano emulsion-based delivery systems represents an innovative method for treating hyperpigmentation. This combination synthesizes the strengths of both technologies, leading to improved efficacy and reduced side effects. Metallic nanoparticles' ability to impede melanogenesis is complemented by nano emulsions' efficacy in delivering these molecules into the skin. When brought together, these technologies produce a superior system to either one alone. Metallic nanoparticles and nano emulsions complement each other by stopping hyperpigmentation and improving skin appearance. Nano emulsions help nanoparticles penetrate deep into skin to reach color-causing cells and the metallic nanoparticles slow down processes that make hyperpigmentation. With more targeted results, it stands a chance for better solutions for those with such condition, with lower risk of adverse effects to that skin. The added stabilization factor helped the product to remain longer at the effective concentration level throughout usage[146]. This is due to increased product stability of metal particles within nano emulsions thereby it can be effectively used through the usage term, and this has helped in maintaining constant and predictable effect upon skin. It also gives other benefits to your skin as it causes less trouble to your skin which would otherwise appear Redness Dryness irritation when used regular treatments of topical skin Lightening product. Many of products containing these particles may have harmful side effects if used in higher concentrations. But using the Nano emulsions product system made use of this technology to deliver an exact amount of concentration from minute nanoparticles in. Such of which, the dosage would not produce bad results, to no result either. And as well will minimize any possibility of skin being stressed or damaged by excess amounts of metal particles. The nanoparticles contained in hybrid nano emulsion systems target specific cells of the skin that lead to hyperpigmentation. These are carried directly into and into skin to penetrate deeply down into specific layer of the skin[147]. It is in this specific level of the skin, where, if it is delivered precisely enough, that we want our skin-lightening effect to actually go to reach, the to. After it arrived in the location it has collected Color and made MITF in color production pathways for reduced expression… it stopped the colored particles or color

to spread throughout to Other areas. It did everything that we wanted, it's worked well. It worked really great. And caused no other side effects to anywhere in the other areas of the body. Furthermore, hyperpigmentation can now be treated efficiently with combined molecules contained in hybrid nano emulsion technology; two or even more medicine contained together in just one product[148]. The small metallic particle can contain any other kind of molecules. For Example, it can be paired with natural plant extracts and pigments inhibiting compounds or the drug acting anti-inflammatory etcetera and such of chemical agents. These kinds of compounds can contribute for broader approach not only stops the pigment, also dealing with sun damages, Stress of the skin, Swelling, Inflammation etcetera and made more comprehensive treatment. While it's still early for this scientific advancement, studies have revealed promising evidence that the combination of metal particles in nano emulsions can be better delivered into the skin, and provide a more prolonged, safe, and effective hyperpigmentation treatment. Further study on optimization of product combination ratios to identify efficient formulation with safe parameters with longer efficacy, and to test it in real human trials will bring innovative products into the market soon[149].

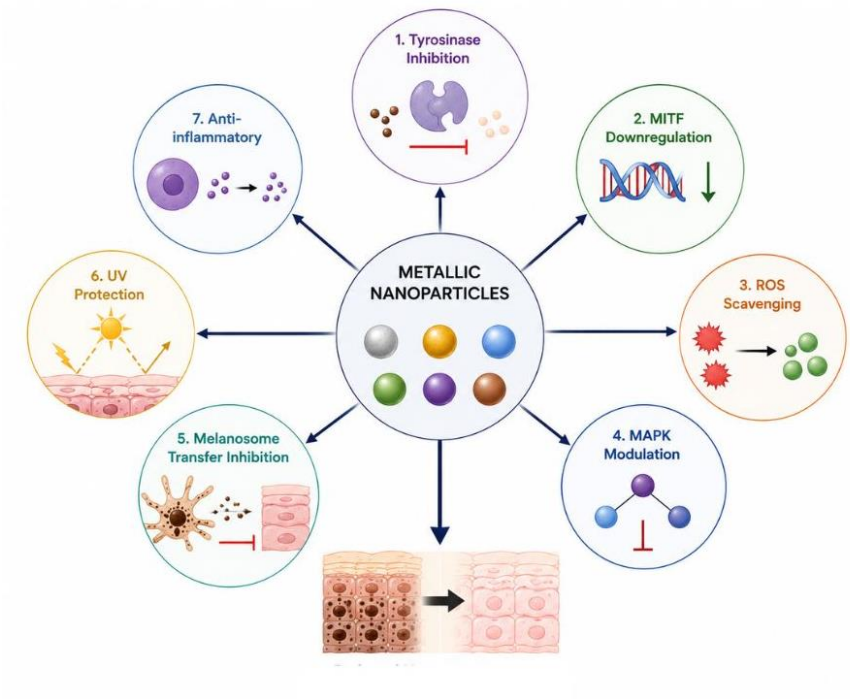


Figure 3. Proposed topical delivery and therapeutic mechanism of nano emulsion-loaded metallic nanoparticles for hyperpigmentation management. Created with BioRender.com.

8. THERAPEUTIC APPLICATIONS OF NANOEMULSION-BASED METALLIC NANOPARTICLES

The ability to transfer the medication through the skin make the nano emulsion-based metallic nanoparticle systems stable, deliver it right on the spot in the melanocytes. Having many such benefits-like inhibiting the tyrosinase activity, antioxidants helping reduce the irritation, acting as an antioxidant thereby preventing oxidative stress, controlled release and lot more, the nano emulsion based metallic nanoparticle systems have found it possible to find the role as a valid alternative of the presently available lotions and creams[150]. Hyper pigmentation the patches of brown appear on face when sun or light causes trauma to the skin, and is predominantly the consequence of stimulation of melanogenesis. The conventional medicines used to treat the disease contain hydroquinone, retinoids, and tranexamic acids which don't always act. They can cause skin to get irritate. However, nano based formulation enables to transdermal drug delivery system that gets the medication into skin easily resulting in reduce pigment, smoother skin which are better than the existing. Post-inflammatory hyperpigmentation The inflammation, the skin can

go through after being burned and etc. may stimulate skin to make pigment thereby resulting hyperpigmentation[151]. So Nano emulsion based formulation integrated with antioxidants and nanoparticles can reduce the process that stimulate the melanin. In addition, they release drug in controlled method that results in less irritation the on the injured skins. Solar lentigines the lesions can occur on skin when you are aged due to exposure of skin in the light many times for many years resulting hyperpigmentation that appears on the lesions. The nano based topical formulation releases many therapeutic agents into skin resulting in reduce the accumulation of melanin in the damaged skin cells, thus preventing them from solar induced skin damage, using of zinc or titanium dioxide nanoparticles can also avoid such damage to the skin because these have the light blocking ability. Freckles The natural spots which are present since a person is born can turn dark when the skin gets under exposure with the light[152]. The topical nano formulations help diminish these spots even without stopping natural process of melanogenesis and also prevent the over secretion of melanogenesis so the dark spots won't appear when exposed to light. Treatment of aging skin Nano emulsion based nanoencapsulation techniques have also been promising in cosmetic and aesthetic practice. It can be a valuable alternative for slowing down of collagen degradation and protecting the skin against oxidative stress, decreasing collagen damage caused by free radicals and enhancing skin elasticity. Anti-inflammatory agents can be released in a controlled manner to reduce inflammation related pigmentation is very common in aged skins, it can also be managed efficiently using dual nano delivery system with antioxidant and melanin inhibitor[153]. For the skin brightening and cosmetic preparations nano emulsion systems are employed to transfer the skin whiten in agent like kojic acid into the skin to improve uniformity of tone. In the coming years it is sure that, with improved nano formulations, it is predicted to introduce various types of personalized Nano delivery system and also the new composite Nano emulsion as the alternative over existing preparations[154].

Table 2. Therapeutic applications of nano emulsion–metallic nanoparticle systems

Disease	Pathogenesis	Nano formulation	Expected Outcome
Melasma	UV + hormones	AgNP nano emulsion	Reduced pigmentation
PIH	Inflammation	Antioxidant nano emulsion	Faster recovery
Solar lentigines	Photoaging	ZnO nano emulsion	UV protection
Freckles	Genetics	Tyrosinase inhibitor nano emulsion	Lightening
Photoaging	ROS	Hybrid nano emulsion	Anti-aging
Cosmetic brightening	Mild melanogenesis	Hybrid metallic NP	Uniform skin tone

FUTURE PERSPECTIVES

The future for treating hyperpigmentation the synergy between nanotechnology, artificial intelligence, precision medicine and cutting-edge biomedical engineering will change the future for treating hyperpigmentation. Although miniscule structures have been effective at aiding the transport of beneficial ingredients through skin barriers, stabilizing potent molecules in delivery formulations and inhibiting the skin's ability to create too much pigment, challenges related to scale-up, patient safety over time, regulatory approval, and formulation production will continue to be hurdles[155]. Future research endeavors should aim to develop multi-tasking platforms that are designed to target oxygen, the cause of inflammation, and that cell signaling factors responsible for melamine synthesis and transport. Ultimately, this can bring better and longer-lasting patient improvements. Machine learning and AI can significantly contribute to accelerating the search for novel nano formulations. Smart AI/ ML algorithms that analyze and predict ingredient formulations can reduce the

trial-and-error required in the laboratory and, consequently, the product cost, even guiding variables such as oil to surfactant ratios, particle sizes, drug-loading abilities, and release kinetics[156]. Personalized treatments at a time where individuals are increasingly seeking personal ways to maintain healthy skin, tiny treatments could be custom-built to individual circumstances depending on a patient's genes, skin type, existing level of pigmentation and environmental exposures. Using exosome technology and specialized switchable nano nozzles will revolutionize the way that hyperpigmentation is addressed. Exosomes hold excellent potential because they minimize the possibility of damaging bodily tissues. Can find the right cells to target making them great for delivering drugs that reduce pigmentation directly to the cells that make melanin. Similarly special tiny mixtures that change in response to things like pH, temperature, enzymes, light or bad things called oxygen species can release drugs in just the right place and amount. This makes the treatment work better. Reduces bad side effects[157].New experimental platforms, including skin models and special devices that mimic the body are going to replace the old ways of testing things in the lab. These new platforms are like real human skin and can help us predict how well things will work how toxic they might be and how well they will be absorbed by the skin. Also using nanotechnology specially making tiny particles from plants is a more environmentally friendly and safe way to make things than using traditional chemical methods. However, to make these new treatments available to people we need to have ways of making them test them thoroughly to make sure they are safe work, with regulators and do well-designed clinical trials to prove they are safe and work well in the long run[158]. If we can do these things we can make treatments that are based on tiny particles and are the next generation of therapies. All these advances can change the way we treat hyperpigmentation now and make it more targeted, smart and effective bringing what we learn in the lab to people who need help with their skin. Hyperpigmentation management is going to be changed by all these things[159].

CONCLUSION

Hyperpigmentation is a chronic and complex syndrome of dysregulated melanogenesis, which is influenced by redox state, inflammation, UV Radiation and transfer of melanosomes. Conventional management strategies are fraught with many limitations including ineffective skin penetration, stability, irritation and recurrence. In this regard, nano emulsions enhance solubility, stability, penetration and targeted delivery of drugs and metallic NPs offer additional anti-inflammatory, antioxidants, photoprotection and melanogenesis modulating activities. Therefore, this synergistic integration of nano emulsion and metallic nanoparticle in hybrid nano emulsion – metallic nanoparticle delivery systems might deliver improved anti-pigmentation benefit with minimized concentration requirement by the virtue of enhanced stability, skin retention and locale of action of encapsulated drug and the delivered metal ion. However, clinical implementation of hybrid nano emulsion – metallic nanoparticle systems need to ascertain the safety/dose/long term dermal exposure, formulator stability, large scale manufacturing process and regulatory issues. Future endeavors like the application of AI in nano formulations, personalize nano delivery, stimuli responsive systems, advanced skin models and the use of nanotechnology based sustainable/green methods can further strengthen these developments. Thus, hybrid nano emulsion-metallic nanoparticle systems offer new pathways for the targeted and more effectual management of pigmentation although, considerable research efforts both pre-clinical and clinical are still required for its effective translational approach.

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