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NANOEMULSION: A NOVEL TRAIT IN THE TREATMENT OF SKIN AGEING

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ABSTRACT: Nanoemulsion system is a promising vehicle due to the powerful ability to deliver the drug through the skin. Researchers have been conducted to prove its potential for the delivery of the drugs used in many skin disorders. Skin is the largest organ and acts as the first line of defense of our body. After a certain period of time, our skin loses tone and elasticity which is called aging. It is the result of programmed senescence and prolonged environmental injury to the skin. The aim of this review article is to provide information regarding the control of skin aging by the nanoemulsion drug delivery system. Novel carrier systems have a lot of advantages when compared to conventional formulations. There are various approaches to preventing skin aging. The most widely used age combating substances in cosmeceuticals are kinetin, Retinoids, sun filters, herbal ingredients (such as resveratrol, turmeric, and green tea), and antioxidants (such as alpha-tocopherol, ascorbic acid, coenzyme Q10 and lipoic acid). In recent years, these molecules have been formulated as nanosized carriers such as vesicular systems, Therefore, nanocarrier such as liposomes, noisome, microemulsions and nanoparticles have been widely investigated as delivery systems for antioxidants to improve their beneficial effects in the treatment of skin aging. In this review, an overview of cosmetic, product-oriented solutions for skin aging is given and different approaches to combat aging are summarized. This review discusses the role of oxidative events of tissue degeneration and aging in general, and for the skin in particular. The mechanisms involved in intrinsic and extrinsic (photo-) aging are described. To prevent or treat skin aging, topical supplementation with antioxidants is regarded as one of the most promising strategies. Overall review says that antioxidants are most commonly used in anti-aging cosmetic products will be reviewed along with the nanocarrier designed to improve their safety and effectiveness.

INTRODUCTION: Nanoemulsion is a type of emulsion which is very fine and metastable in nature, the size of the droplets is smaller than the 100 nanometres. Based on the process used for the preparation of nanoemulsion their structure is identified.

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There are several methods used for the preparation, including spontaneous emulsification followed by phase inversion temperature emulsification, phase inversion and with the help of high shear device [1].

This process of preparation allows good control over the size of the nanoemulsion droplet size and many options of composition. This nanoemulsion drug delivery system has more importance in the transdermal application due to its direct contact with the skin barrier, importantly the oil/water type of emulsion with the oil phase act as the carrier for the bioactive molecules using increased active molecule. This type of colloidal drug targeting

system will be used to absorb the drug molecule to select on bioavailability enhancement, high stability and to minimize the adverse effect [2]. Nanoemulsion distribution of drugs through percutaneous absorption and local limitation to skin increase its effectiveness and systemic reaction. Sometime it may cross BBB (blood-brain barrier) to show its multiple applications in the central nervous system.

According to the literature, nanoparticles increases the active site by disturbing the lipid barrier from the distinct spaces. As per the report, nanoemulsion has more solubilization ability than emulsion and suspension with long-time shelf life, recent improvement of delivery to transdermal skin formulation such as transparent gel and emulgel with havening better patient acceptance and increased effectiveness [3]. Even though it has better application, the topical formulation is restricted because of low spreadability and low viscosity hence the researcher solved this problem by transformation of nanoemulsion into nanoemulgel [4]. Nanoemulgel is the modified form of nano-emulsion either with oil in water or water in oil type incorporated with the gelling agent with better improved characteristic features with the nanoemulsion such as less irritation of the skin, enhanced permeability [5].

Methods used for the Preparation of Nanoemulsion: Preparation of Nanoemulsion requires a huge amount of energy or surfactants sometimes both because it is a non-equilibrated system and hence for the formulation of Nanoemulsion either high energy or low energy system can be utilized Even though high energy level is widely used low emulsification method gives attraction [6]. Energy consumed by the preparation of Nanoemulsion is higher than the energy used by the macro emulsion. The surface tension of the oil phase and the water phase is reduced by the use of surfactants; also its effects on interfacial dilatational theory.

Adsorption of surfactants from the bulk will restore the equilibrium, but it takes time due to inefficient equilibrium with polymeric surfactants [7]. The continuous phase requires an excess amount of surfactants due to which new surface area with Nano-droplets is coated during emulsification, thereby preventing the coalescence. This excess is in the form of surfactant micelles in the continuous phase and these micelles separated to form monomers which adsorbed on the surface various emulsifier are used in the preparation of Nanoemulsion to reduce the coalescence during the emulsification processes [8].

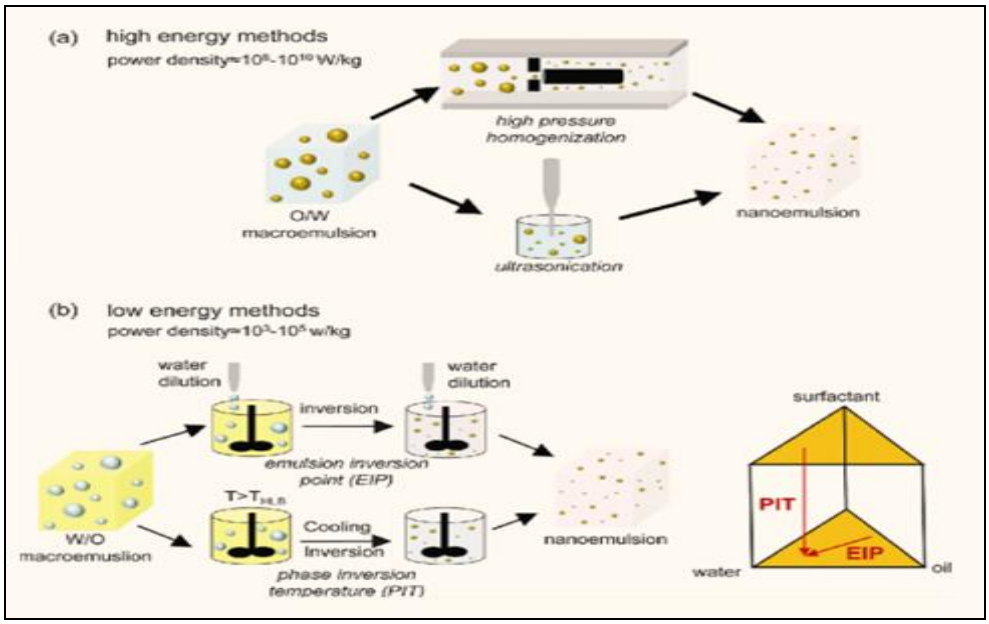

FIG. 1: THE SCHEMATIC REPRESENTATION SHOWS THE PREPARATION OF NANOEMULSION USING (A) HIGH ENERGY METHOD (B) LOW ENERGY METHOD

Low Energy Method: This mainly based on phase transition and intrinsic physical and chemical properties of surfactants and co-surfactants and oil to obtain emulsion with nanosized droplets. This

method is also named as condensation method. Depending on emulsification processes such as phase transition. This phase transition takes place due to the sudden changes in curvature of surfactant can be achieved [9] by changing the non-ionic surfactant curvature using temperature and constant composition the well-known phase inversion temperature in other cases this low energy method was improved based on characteristics of constituents and phase behavior to induce the generation of ultra-small droplets [10].

These methods consist of phase transition, phase inversion temperature method and self-emulsification methods. This method uses the stored energy for the formation of droplets from the system and by varying the different parameters which will greatly affect HLB value (hydrophilic and lipophilic balance) of the system such as temperature and composition [11].

High Energy Method: The principle used in this method is the breakdown of larger droplets into smaller ones to form nanoemulsion with required droplet size using mechanical energy known as micro fluidization. The very small size of the droplet is formed using homogenizer which is having high energy and physical and chemical properties of constituent phases, this method is not appropriate for unstable forms such as protein and mainly used for producing food-grade nanoemulsion [12].

Characterization of Nanoemulsions: Nano-emulsion characterization implicate various components such as formulation isotropic content uniformity, methodological assay, physical appearance, pH of the system, surface tension, *etc*. with respect to the physical parameters which effect on the composition also to carry out tests such as physical and chemical which is associated with the oral dosage form [13] details about the interaction of different compositions can be obtained by the (DSC) Differential scanning calorimetry and the polarization microscopy can observe isotropy of the nanoemulsion. The visual analysis estimates the evaluation of self-nano-emulsification by determining the distribution of droplet size.

Equilibrium achieved [14], the turbidity quantification identifies this equilibrium achieved by the dispersion and reproducibility of the procedure. Size of the nanoemulsion droplets is calculated by various technologies such as static light scattering and dynamic light scattering *etc*. to identify whether a nano-emulsion is oil-continuous or water continuous and also phase inversion process conductivity measurements are used [15]. To observe both structural and dynamic properties of nano-emulsion dielectric measurement electron microscopy, cooling is needed for the maintaining of the structure as well as to reduce the possibility of artifacts is a very useful tool. For characterizing the efficiency of emulsion droplet polarity is very prominent .polarity is also the main factor of the oil droplets, it indicates the attraction of a drug molecule to oil or water and the type of force arises fast release of drug substance is also depend on the polarity [16]. Charges present on the surface of oil droplets is another factor which is to be estimated normally it is –ve because of fatty acids, the addition of cationic lipid in the concentration of 1-3 percentage will produce cationic nanoemulsion [17].

Morphology: Transmission electron microscopy and scanning microscopy is used for the determination of the morphological characters of the nanoemulsion. This scanning microscopy will show the 3d image of the droplets at various magnification and appropriate accelerating voltage such as 20kv samples are being tested, a defined analysis on the morphology of formulation is produced by SEM [18] to obtain a natural analysis result of shape and morphology image analysis is implemented. The formulation is negatively cooled with one percent of phosphotungstic acid over the piloform coated with copper and observed through the TEM at the proper voltage. The size distribution of micrographs of transmission electron microscopy can be carried out with the help of digital image processing program advanced methods such as x-ray, neutron scattering are commonly used to elucidated the structure and behavior of nanoemulsion [19].

Determination of Viscosity: It is one of the most prominent parameters for the physical and chemical characterization of nanoemulsion. Many instruments are used to measure the viscosity in which Brookfield is majorly used for nanoemulsion formulation. Estimating the viscosity gives the idea about whether the emulsion is oil in water or water

in oil type [20] and recently strainmeter is used for determining the surface tension, viscosity, angle of contact, dipole, size of the particle of the nanoemulsion viscosity of ramipril nanoemulsion is measured by using Brookfield is less than 21cp with least viscosity of 10.68 cp viscosity is very prominent role in stability and effective drug release, in semisolid dosage form, liquid including nanoemulsion viscosity change method is used to assess the stability [21].

***In-vitro* Skin Permeation:** For the transdermal application, to produce nanoemulsion with good drug release format Franz diffusion cell is used. The rate of the extent of skin penetration by the released product can be examined using confocal scanning laser microscopy instruments [22]. *In-vitro* drug release can be estimated by dispersing of formulation in the Franz cell which is having donor compartment with a membrane and controlling the view of drug in capsulated form in receptor chamber which is filled with the phosphate buffer and a stirrer at a speed of rotation 100 rpm after some interval samples are withdrawn and filtration is carried out then using HPLC drug release is estimated at peak absorption of drug-using diffusion cell membrane another important technique of *ex-vivo* experiments are conducted to study the release pattern [23]. The skin part from the ear or stomach is cut and cartilage or fats are detached and kept in diffusion cell which is filled with receptor solution. Then samples from the vesicular formulation are applied on the skin and the operation is started.

Preparation is taken out from the medium and replaced with the formulation used to analyze for permeation using HPLC. Semipermeable membrane such as cellulose may be replaced in the place of skin for estimating the *in-vitro* release study, flux across the skin is calculated using J=Ddc/dx in which is known as the coefficient of diffusion, the shape of the molecule flexibility, c is the concentration of the molecule, x for spatial coordinate [24]. Dermatopharmacokinetics which is also known as an in vivo release study is conducted by administering the formulation to the live animals. After the sometime sample is taken out and then centrifuged, using HPLC instruments plasma concentration is determined to study the bioavailability of the preparation report obtain from both *in-vivo* and *in-vitro* studies are extra plotted in graph [25].

Stability of Nanoemulsion: Nanoemulsion stability studies are mainly based on the surfactants used in the preparation, composition of the formulation, and particle size of the nanoemulsion, in which surfactants play a major role in the formulation by reducing the interfacial tension among the two different compartments to obtain the very small droplet size [26]. Against heating, storage for a longer time, ionic strength emulsifier used in nanoemulsion will impact on the stability. for stabilizing the emulsion, surfactants are used in many ways those are ionic surfactant which produces charge on surface and non-ionic surfactants design a steric barrier with large molecular groups. Furthermore, larger droplets have influenced by more gravitational force than the smaller molecule [27].

With respect to that of flocculation, sedimentation, creaming this nanoemulsion possesses the more stability because of its particle size characteristic particles which are smaller in size minimum sticking and more stability than the flocculation which coincides with steric stabilization for which nanoemulsion is naturally blocked. Meanwhile, Ostwald ripening is an important destabilization mechanism for them due to their droplet sizes [28]. Hence, it causes the more restriction for their use of applications the rate of Ostwald ripening for the nanoemulsion is reduced by various techniques such as a less soluble in the dispersion medium as the internal phase is productive, as reducing the hydrocarbon solubility in aqueous phase the stability of nanoemulsion will be prominently increased with respect to Ostwald ripening in addition to that lipid such as triglycerides which are less polar in nature form insolubility in aqueous phase [29]. Hence, it gives a barrier to the Ostwald by using the high molecular weighted oil rate of Ostwald ripening is decreased because the molecular weight of the oil is an important to factor there are many studies are conducted on the emulsion stability. according to the scientist stability of nanoemulsion can be observed with the help of PIT method and reported that after the phase inversion takes place heating, cooling final temperature is reported which shows maximum influence on the distribution of size of the particles;

also they observed that sufficient temperature for the storage which is purely based on surfactants these nanoemulsion are more stable form with very smaller sized particle having lesser polydispersity indices hence emulsion which is stored at standard temperature keep their small particle size and maximum stability [30]. All studies related to the influence of various salts such as inorganic on PIT, electrophoretic properties with long-time stability they found that by salting out of salt process in aqueous medium nanoemulsion having emulsifier with more PIT could be prepared easily which gives an optimal temperature by lowering of the PIT methods and suggested that for the instability of nanoemulsion Ostwald ripening is the main cause [31].

Skin Aging: Skin aging is raising the wide range of human population mainly in the industrial region from the 21st century. The effect of aging in the individual is seen on the surface of the skin with high wrinkling, sagging with more laxity over the dermis. Which is contemplated as unacceptable for cosmetic reasons, it is also related to the physical skin disease [32].

According to the report skin aging will be interrupted by the functioning of the barrier surface which leads to dryness in the appearance of the skin surface and with an increased chance of skin-related disease. Mechanism of skin aging is main to advance the cosmetic products related to the skin which reduces the aging of the skin and the unpredictable effect of aging. Cause for skin aging may produce by either intrinsic or extrinsic component. The main reason for the extrinsic skin aging is ultraviolet exposure and smoking leads to a decrease in structural activities [33]. The changes that occur are epidermal skin becomes less dense caused due to the depletion of vascular nature and hydration of skin without affecting the number of layers in the epidermal barrier. The epidermal opacity is decreased by nearly 6.4 percentages throughout every decade of skin aging and this causes a reduction in the mast cell and fibroblast. Lesser the amount of keratinocyte proliferation and decreased amount of glycoprotein leads to surface thinning of skin [34]. CD44+ve cells are outlined to have a major regulatory part in skin proliferation and upon skin aging, hyaluronic acid and homeostasis are maintained.

Surface thinning of skin dermis is caused by less production of collagen, elastin, and hyaluronic acid as a result of a decreased amount of total fibroblasts.

The change in extracellular related to skin aging has been assigned to circulating glucose and glycation end-product(AGEs) which is produced as an outcome of non-enzymatic glycation of amino groups on reducing sugars of protein which effect on changes in the structure of extracellular matrix [35]. With more calcification in the skin, aging leads to the structural modification in the dermis, degradation of elastic fibers, and variation in the organized state of collagen structure as they are not organized with aging. Aging is a biological and complex theory, which is mainly essential because of its social impact [36].

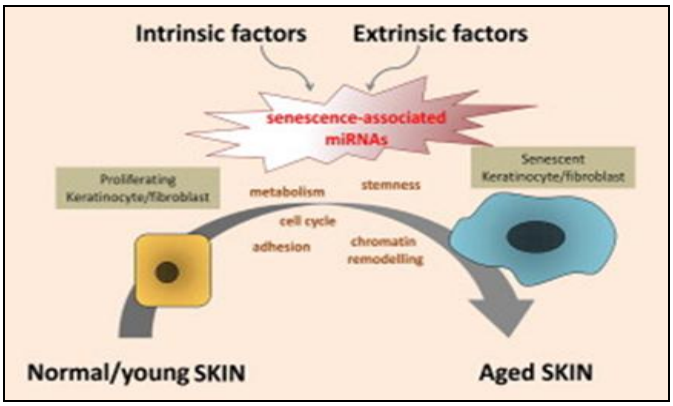

FIG. 2: THE SCHEMATIC REPRESENTATION SHOWS THE DIFFERENCE BETWEEN INTRINSIC AND EXTRINSIC FACTORS AFFECTING THE SKIN AGING

Outcomes of skin aging are both external and intrinsic but depending on the external skin appearance they can be monitored or controlled. To analysis it by competitively characteristic of the skin during the aging process with many non-invasive or invasive advances in the biological engineering concept is helpful. Meanwhile, Transdermal water loss is used for identifying the modification in the integrity of skin barrier, TEM is explained as the amount of water that flows through the skin epidermis and nearby areas by processes such as diffusion and evaporation. The electrical capacity of the skin is measured with a skin chronometer along with the amount stratum corneum hydration is measured. A non- destructive method for analyzing the molecular compounds is compared with the changes that occur in collagen properties of skin such as fragmentation, solubility,

positioning of fibers in photoaged with skin aged chronologically [37].

Intrinsic Aging: Intrinsic aging causes through the crossing of time. This is also known as chronological aging or it may also be considered as endogenous aging, affected by many internal processes that occur inside the body containing a cellular level of metabolism, changes in the hormone and some of the genetic factors. Inside the skin, mass production of collagen fibers will retard hence elastin shows spring in nature. The cells which are dead will not shed rapidly in turn formation of new skin may slow down gradually [38].

This type of aging process mostly will observe in old age peoples and will affect all skin parts. Skin becomes thin, transparent and dry which indicates wrinkles and irregular hair growth, unable to sweat sufficiently and disrupted from loss of subcutaneous fat tissue which finally leads to narrow cheeks and eye sockets inadequate sweat and decrease of the nail plate. This manifestation changes according to body site [39].

This aging phenomenon varies per traditional group but the degree of pigmentation and contributing factors are not identified yet. The important process related to intrinsic aging is having lesser reproducing capacity of cells and high degradation of the extracellular matrix this reproducing capacity will gradually decrease with time. These will more likely acts on keratinocytes, fibroblasts, and melanocytes; this phenomenon is known as cellular senescence. Non-dividing cells are visible in the maximum portion of aged skin. This act of cellular aging is associated with the more number of cell divisions that somatic cells can undertake, at the chromosomal ends a small part of the telomere is lost while every cell division. After a while telomeres become critically short, and the DNA loss during subsequent cell divisions can affect areas of essential genes and lead to loss of somatic cell function [40].

Upon skin aging, the factors included in the aging process like an extracellular matrix of the dermis will be degraded with the greater enzyme expression. In an aging fibroblast increase in (MMP), metalloproteinase is observed and expression of MMP inhibitors (TIMP) is reduced. This type of process is activated by reactive oxygen species and antioxidants such as quercetin will bring down the event. Furthermore, continuous oxidative destruction in gene coding leads to components such as collagen and elastin to reduce the expression in aged skin [41].

Extrinsic Aging: One of the main reasons for extrinsic aging of the skin is oxidation which can be caused by both environmental and other exogenous factors. Radiation from the sun is one such oxidative factor and is the primary cause of extrinsic aging of the skin. Apart from solar radiation, extrinsic aging is also caused by cigarette smoke and other polluting factors. Extrinsic aging of the skin due to such exogenous factors is permanent damage to the skin [42].

Solar radiation is the major reason behind extrinsic aging and is commonly referred to as photo-aging which accounts for approximately 80% of facial aging. The radiation from the sun exposes the skin to UV radiation which over a period of time results in skin aging. The resultant aging is gradual and the frequency, duration of exposure and intensity contribute to the rate of degeneration [43].

Exposure to both longer wavelength UV radiation (UVA) and shorter wavelength UV radiation (UVB) can cause skin aging and the extent to which the radiation penetrates the skin depends on the wavelength. Prolonged exposure to UVA damages the epidermal connective tissues and thereby can potentially lead to skin cancer, whereas UVB impacts include tans and sunburns. The amount of UV radiation to which skin is exposed and the status of skin pigmentation determines the acuteness of photo-aging [44].

Photo-aging primarily occurs on the upper portion of the hands, neck and the face. This not only causes cutaneous damage but also results in neoplastic lesions. Extrinsic aging impacts the skin in many ways, which vary from being as simple as dryness, volume loss, deep wrinkles along with fine lines, roughness, bulges, the formation of dark spots to as complex as skin cancer. Furthermore, if the impact is severe, the blood vessels may bleed internally, resulting in the formation of purple spots and even the wound healing capabilities at the affected spots are impaired [45].

The extent to which the skin aging is apparent depends on the type of the skin with the aging being predominantly visible in individuals with skin type I and II (fair skin individuals) and not as much in individuals with skin type III or more. Depending on the complexity, the extrinsic aging factors such as sunlight, nicotine, various muscular movements as well as food habits, sleeping position are controllable to varying extents (Singh G), and the resultant changes at the molecular level have been extensively researched and understood in the recent times [46].

Novel Colloidal Drug Delivery System for Skin Aging: These nanoemulsions play a prominent role in the colloidal drug carrier for the pharmaceuticals, majorly in the skin application. This type of delivery system carries a drug molecule into the skin surface. This is a deal for crossing the skin barrier for topical delivery for penetration of drug molecule which is based on the physical and chemical properties of the drug delivery system. According to the active ingredient used and patient choice and importance drugs are used for the delivery system. with nanoparticle size are these nanoemulsions are more advantageous for skin treatment with the use of active pharmaceutical ingredients which is having control over the size of the droplets, the capacity to dissolve lipophilic drugs extended-release of a lipophilic and hydrophilic drug.

Hence, it enhances the hydration and visco-elasticity of the skin surface, due to nanoparticle size of nanoemulsion formulation when it is applied on skin surface it improves the permeation of drug than compared with different topical formulation [47]. This colloidal and topical drug delivery prefers more application towards the patient's compliance, moreover facility for the delivery, avoiding the first-pass metabolism, risk and inconvenience occurs by intravenous therapy this topical drug delivery is very useful.

Topical drug delivery is another method to oral medication if there cause poisoning it can be removed easily, this topical administration is useful for the self-administration so that the cost of the treatment will be reduced the disadvantages of this topical application is skin itching, contact dermatitis because the preparation contains hydrophilic molecule mainly in emulsion formulation [48]. Other preparation such as liposome, noisome, ethosomes, lipid carriers are more useful in the treatment of the topical application as antipsoriatic drugs, these nanoemulsions are well characterized and promising topical drug delivery for the patient with psoriasis. Nanoemulsion has improved topical delivery characteristics *in-vitro* and *in-vivo* transdermal permeation for the antipsoriatic drugs over liposomes and ethosomes.

This nanoemulsion enhances the efficiency of the drug molecule to cross the permeable membrane along with skin, in that hydrogel nanoemulsion provides more stability and best suitable for iasis, which is prepared by phase titration of aqueous method [49].

Antioxidants in Skin Aging: The role of antioxidant is most important in the skin aging and its treatment, there is mainly two types of antioxidants are used in this aging named as endogenous and exogenous antioxidants [50].

TABLE: 1 ANTIOXIDANT IN TREATMENT OF SKIN AGING

Antioxidant compound/nanocarrier	Antioxidant Obtained from the sources	Endpoint studied for topical application/ proposed use
Vitamin C (ascorbyl palmitate)	Sources obtained are vegetables and fruits	Photoaging, erythema, phptocarcinogenesis[53]
Selenium	Wheat, soybean	Erythema, phptocarcinogenesis[54]
Silymarin	Milk thistle	Immunosuppression photocarcinogenesis [55]
Resveratrol	Grapes seed, nuts,	Erythema photocarcinogenesis[56]
Pycnogenol	Extracted from the bark of maritime pine tree	Inflammation, immunosuppression[57]
Vitamin A (retinols)	Wheat, vegetable	Photoaging[58]
Vitamin E (α tocopherol acetate)	Vegetable oil, seeds, nuts, meat	Erythema, Photoaging[59]
Caffeic acid [ferulic acid]	Coffee beans, propolis	Erythema, immunosuppression[60]
Green tea polyphenols[epicatechin	Fraction isolated from tea	Photoaging, erythema[61]

Endogenous Antioxidants: These antioxidants are mainly enzymes that include catalase, glutathione peroxidase, and oxide reductase. These prevent the oxidants by catalytically hence decrease the

oxidative damages that occur during the process and another important endogenous antioxidant is coenzyme CoQ10 also called as Ubiquinone which is lipophilic in nature found in every human cell as mitochondrial respiratory chain product, helps in preserving the dermal homeostasis which is found to be present more in epidermal region than in dermal region. CoQ10 related to vitamin E prohibits the collagenase expression obtained by fibroblast with respect to UVA MMP-1 and collagenases are playing a vital role in the aging of the skin. Byob serving the ability to enhance the basement membrane formation from the CoQ10 such that keratinocytes, fibroblast it is reported that CoQ10 is was more useful in skin aging process [51].

Exogenous antioxidant vitamin E For the skin preparations this is one of the best-known antioxidants. There is about 8 isoform for this vitamin E, which are lipophilic, found in the seeds, meat vegetables in which tocopherol is biologically active isoform [52].

Role of ROS/Free Radicals in Skin Aging: Reactive Oxygen Species (ROS) are produced in the mitochondria as by-products of the aerobic metabolism associated with an electron transport chain. When an electron combines with each of the oxygen molecules, it results in the production of a reactive superoxide anion which is commonly referred to as ROS. There are various sources for the production of ROS such as the proteins present in the endoplasmic reticulum and peroxisomes, enzymes such as lipoxygenases, cyclooxygenases, nicotinamide-adenine dinucleotide phosphate (NADPH) oxidases, *etc*. The chromophores in the cell, when exposed to UV radiation get excited by absorbing energy and lead to the production of ROS and other oxidation products. Increased production of ROS may adversely affect regular cellular functions [62].

ROS is one of the primary contributors to skin aging. They cause an increase in the number of enzymes that are responsible for the continuous degradation of the dermis and the extracellular matrix. The ROS are found to increase the amount of Matrix Metalloprotease (MMP) when compared to that of MMP inhibitors, thereby adversely affecting the amount of extracellular matrix. Cells that are affected by this lose their ability to replicate and become senescent. The process of senescence is stimulated by the ROS which in turn results in skin aging. While being one of the major reasons for skin aging, the ROS also play a role in regular functions such as proliferation, preventing tumors, signaling, fight against pathogens and oxygen homeostasis. It is found that low and medium level of ROS in the cells causes mutagenic effects and senescence respectively, whereas when the ROS levels in the cells are high, cell death occurs either by necrosis or apoptosis [63].

Exposure of a cell to UV radiation and heat as well as neutrophil degranulation during cell inflammation leads to the production of ROS and consequently, the cell is subjected to oxidative stress. This stress causes the tissues to degenerate and thereby causes tissue aging. Production of ROS damages various parts of the cell such as DNA, RNA, mitochondria and associated proteins. The damage of DNA by ROS is either due to a direct reaction with the DNA bases or an indirect reaction because of the oxidation of lipids. This damage not only causes abnormal cell functioning but might as well play a role in causing cell cancer [64]. Since RNA is a one stranded molecule consisting of numerous exposed areas, it is more susceptible to a ROS attack and may lead to the production of abnormal proteins as well as hamper normal functionalities of the enzymes in the cell. The production of ROS leads to "Common Deletion," which refers to the deletion of a large number of mitochondrial DNA (mtDNA). This affects the dermis adversely and thereby plays a role in skin aging. ROS also causes damages to connective skin tissue such as collagen, elastin, and glycosaminoglycans. It has been found that an increased level of ROS causes loss of recoil capacity, loss of tensile strength, wrinkles, skin dryness, reduced wound healing capabilities and excessive fragility [65].

Although, the ROS is found to damage the cellular functions in numerous ways and contribute largely to skin aging, the fact that ROS is beneficial as well cannot be ruled out. Experiments conducted on animals to study the effect of oxidative stress due to ROS reveal that there are several benefits to the human body in the presence of ROS in terms of health and lifespan.

Interestingly, a controlled increase of ROS production resulting in low oxidative stress is found to provide resistance to tissue degeneration and aging and this phenomenon are known as mitohormesis [66]. *In-vivo* studies on some mice have also shown that while there is an increase in tissue damage due to oxidative stress, there is no reduction in the lifespan, reiterating the fact that there exists a complex connection between ROS, aging and lifespan in an organism [67].

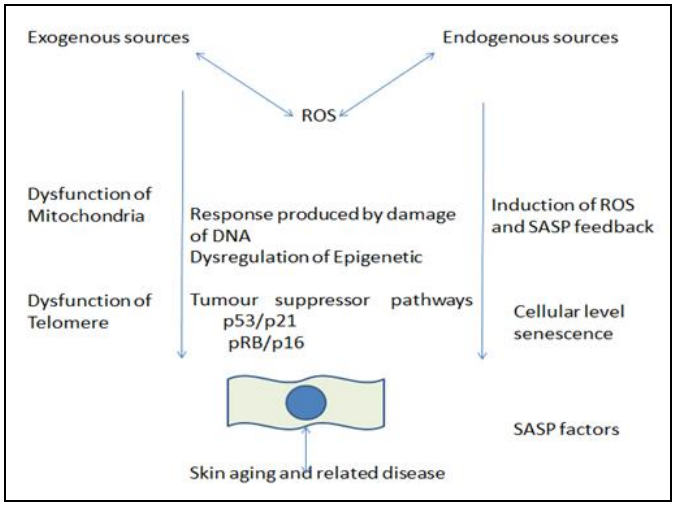

FIG. 3: ROLE OF ROS IN SKIN AGING PROCESS

Treatment for Skin Aging:

Sunscreens: These are the agent used for the protection of skin from the damage of UV radiation, to reduce the sunburns, and to change the pigmentation. Hence, they lower the skin aging. According to recent food and drug administration guidelines stated in the year of 1999 contains 16 sunscreen agents, in which 14 products are organic filters now it is called chemical filters, and the two more products contain titanium and zinc oxide it inhibits the penetration of ultraviolet rays on the skin. Hence, because sunscreens are used in many cosmetic products it is necessary to know that for which type of skin is to be protected. And FDA stated that labels present on the sunscreen product should contain factors such as SPF [68].

Laser Procedures: It is used to treat the wrinkles and other complications of the skin with respect to mouth and eyes these laser rays affect the cell by producing the radiation later it is absorbed by the cell through the water. Many methods such as cutaneous laser surgery and treatment are used to diagnose the aged skin, which includes hyperpigmentation, dermal remodeling, either ablative or non-ablative laser treatment are used for the skin aging and to greater the collagen synthesis [69].

Photodynamic Therapy: Recent clinical development has stated this therapy which includes the use of 5-aminolevulinic acid which seems to be creating prominent variation in the molecular level to modify the skin-aging appearance. They calculate the molecular variations in both dermal and epidermal cell changes related to this theory in an individual sample, which is extrinsically damaged forearm skin with clinical proof. This photodynamic therapy was related to epidermal differentiation with proof more than a 5-fold increase in Ki67 and more than 1.4 fold which increase the thickness of the epidermis. Molecular identity should not be explained in the clinical report of the patient. This therapy status statistically important quantitative molecular variation related to the modified appearance of the dermis [70]. Hence, it gives the promise of repairing and reproducing and may useful diagnosis for the skin aging in the future. Another important technique to treat the skin aging with the clinical evidence is Microdermabrasion which includes the spraying of the crystal molecule to corroded skin into a loop system that is closed consisting of a vacuum intended used in skin debris and molecules. The deepness of the abrasion is based on the variety of crystal used and the number of passes the operator creates through the treated area and the model of machine. This process is explained temporarily to cure many skin disorders such as pigmentation, wrinkles and skin texture irregularities [71].

CONCLUSION: Aging of the skin is a biological process that is caused by many internal and external sources, malnutrition and stress. The problem related to skin aging is dryness, wrinkles by conventional and novel ways are used to prevent skin aging problems. Dosage forms such as emulsion, solution, gels is well accepted for the topical drug delivery which is having some limitations in terms of safety and efficacy of the treatment. To overcome this problem novel delivery such as antioxidants are using carrier system these having increasing skin penetration. Drugs such as resveratrol, tocopherol are more studied for the novel carrier system such as solid lipid carriers.

By using liposomes, microemulsion a nanoemulsion use of plant component in cosmetics are studied in which nanoemulsion are most effective cosmetics and preferred over the distribution of active ingredients to specific skin layers by using vesicular system transdermal epidermal loss can be prevented, sunscreen ingredients are incorporated in the microcapsules and also lipid core Nanocapsules have been shown to be great potential systems for local application of low water solubility compound such as resveratrol to skin. Reasons for choosing these approaches in cosmetic formulations are as follows: there is a need for a formulation in which the structure of a substance, mixture or plant extract, exhibits desirable properties *in-vitro* conditions, is supported by *in-vivo* studies and can be delivered to the targeted site without chemical modification or altering its structure. New generation cosmeceuticals based on developing production technologies and the use of novel delivery carrier systems in cosmetic formulations offer advanced cosmetic care alternatives. The development of cosmetic products using advanced active cosmetic ingredients, the increased use of natural source raw materials as cosmetic ingredients, and the use of new, nanosized carrier systems in cosmetic formulations aim to meet the increasing societal demands and expectations of cosmetics.

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