IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Development Of Neurocosmeceutical Formulation Targeting The Skin–Brain Axis: A Review

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ABSTRACT

The field of neurocosmeceuticals has emerged as an innovative advancement in cosmetic science, integrating concepts from neuroscience, dermatology, and pharmacology to target the skin–brain axis. This review explores the formulation and functional mechanisms of neurocosmeceuticals designed to regulate the bidirectional communication between the central nervous system and the skin through neuroendocrine and immune pathways. The skin functions as a neuro-immuno-endocrine organ that responds to psychological stress via activation of the hypothalamic–pituitary–adrenal (HPA) axis, resulting in increased cortisol production, oxidative stress, inflammation, and impairment of the skin barrier. These changes are associated with various dermatological conditions such as acne, psoriasis, atopic dermatitis, and premature aging.Neurocosmeceuticals incorporate bioactive agents including peptides, adaptogens, antioxidants, and plant extracts to modulate neurotransmitter activity, reduce neurogenic inflammation, and restore skin homeostasis. The application of advanced drug delivery systems, such as liposomes, nanoparticles, and microemulsions, enhances the stability, penetration, and targeted delivery of active ingredients.Despite their promising potential, challenges remain, including insufficient clinical validation, lack of standardized evaluation methods, formulation instability, and regulatory uncertainties. Future developments emphasizing personalized skincare and technological advancements are expected to expand the scope of neurocosmeceuticals. Overall, these formulations represent a novel and holistic approach for managing stress-related skin disorders by addressing both physiological and psychological factors influencing skin health.

Keywords -Neurocosmeceuticals; Skin–brain axis; Psychodermatology; HPA axis; Neurotransmitters.

I.INTRODUCTION

Cosmetic science has seen a revolution of sorts, moving beyond traditional cosmetic products and entering into the realm of what is called cosmeceutical formulations that are a combination of cosmetic and pharmaceutical properties. Not only are cosmeceuticals meant for enhancing appearance but they act by virtue of their biological properties, dealing with physiological conditions like aging, hyperpigmentation, and inflammation [1]. With the emergence of the relatively new field of neurocosmetics, an entirely new perspective has been added to this domain through the fusion of neuroscience with dermatology [2].

In recent years, there has been an increase in the scientific interest in the skin-brain connection because of its function in ensuring the balance of the skin's physiological state due to the interactions that occur within a complicated neuroendocrine and immune system. Skin can be considered an important neuroendocrine organ that is able to produce and respond to neurochemicals, neuropeptides, and hormones [3]. Through the mechanism of bidirectional communication, mental processes can affect the physiological function of the skin, creating a link between emotional and physical states. Such neurotransmitters as serotonin, dopamine, and substance P, as well as cortisol, affect skin physiology[4].

It is well established that psychological stress is one of the main triggers for numerous skin disorders, and stress activation results in HPA axis activation, producing higher levels of cortisol, oxidative stress, inflammation, and skin barrier disruption [5]. These alterations have been found to be related to several types of skin disease, such as acne, hyperpigmentation, atopic dermatitis, and accelerated skin aging [6]. In particular, stress-related inflammation promotes melanogenesis, causing hyperpigmentation, whereas excessive oxidative stress damages skin cells and fibers, thus inducing aging [7].

Here, the concept of neurocosmeceuticals has been introduced as an effective solution, with the intent of addressing the skin-brain axis in order to achieve a balanced state of the skin. The formulations of neurocosmeceuticals contain biologically active compounds like phytochemicals, antioxidants, peptides, and adaptogens that have the capability of modulating neurotransmitter functions, reducing stress-related harm, and restoring balance in the skin [8]. Moreover, new developments in formula design technology, such as nanosomes and liposomes, have increased the potency and effectiveness of the active compounds contained in neurocosmetics [9].

Though there have been many developments made in the field of neurocosmetics in recent times, still, issues related to standardization, clinical validation, and regulatory acceptance need to be addressed. However, given the increased scientific knowledge regarding the relationship between the brain and skin, the prospects of formulating neurocosmeceuticals are quite promising. Hence, the aim of the current review is to discuss the formulation of neurocosmeceuticals with regard to their mechanism of action, ingredients used, and possible application in stress-induced skin disorders.

Concept of Neurocosmeceuticals-

The neurocosmeceutical is a relatively new category of cosmetic products which can alter the way in which the skin and nervous system interact. Unlike regular cosmeceuticals which affect skin structure and biochemistry, neurocosmeceuticals focus on regulating skin homeostasis and emotion-related signaling processes. The rationale behind the development of neurocosmeceuticals rests on the premise that, besides its role as a protective layer, skin is a neuro-immuno-endocrine organ capable of reacting to psychological stimuli.

In recent years, research conducted in the area of cosmetics has revealed the potential of incorporating ingredients into skin care products in order to stimulate sensory receptors, thus enhancing both skin health and overall wellbeing [10].

II.THE SKIN-BRAIN AXIS

The skin-brain axis is a multidirectional communication system involving a close link between the central nervous system and the skin via neurological, endocrine, and immunological channels. Historically, the skin has been regarded mainly as a shield against external influences; nevertheless, contemporary studies have demonstrated that the skin is a functional neuro-immuno-endocrine organ that not only receives but also transmits information.

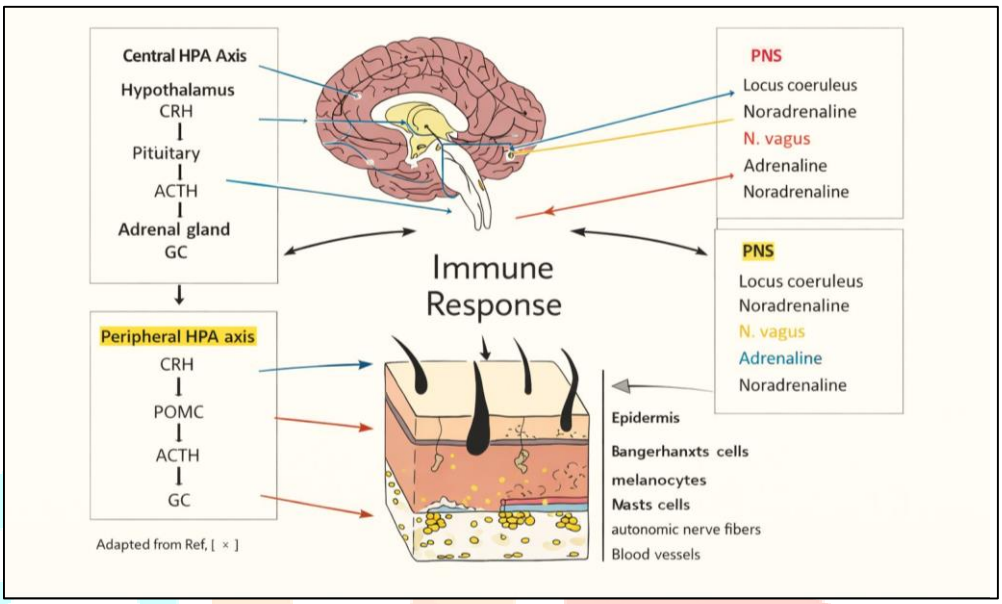

Figure 1: Schematic representation of the skin–brain axis showing the central and peripheral HPA axis, immune response, and communication between the brain and skin

Source: Adapted from Weiglein A et al.2022[49].

This figure demonstrates the bidirectional communication between the brain and skin mediated through neuroendocrine and immune pathways. The central and peripheral HPA axes work together to regulate stress responses and maintain skin homeostasis.

The relationship between the skin and brain tissues develops in utero, as both organs are derived from the ectoderm. For this reason, there exists a continuous physiological interconnection between them throughout life. The skin has sensory nerve fibers, neuropeptides, and hormonal receptors that help it react quickly to stimuli of a psychophysical nature. On the other hand, messages emerging from the skin impact brain functions and affect emotions[11][12].

- Role of the Nervous System-
  The nervous system is an important factor involved in the process of communicating between the brain and the skin. There are numerous nerve endings present in the skin that produce neuropeptides like substance P and calcitonin gene-related peptide (CGRP), which help control various biological activities such as inflammation, vasodilation, and sensory activities.
  Exposure to external stimulants like touching, thermal, and painful sensations is mediated through nerves from the skin to the brain. The brain can affect skin activities by producing chemicals to control cellular behavior. Neural control is critical for skin homeostasis and stress-induced activation [13].
- Role of the Endocrine System-
  The role of the endocrine system in the skin-brain connection is predominantly that of hormonal messaging. Among the main signaling pathways responsible for this process is the hypothalamic-pituitary-adrenal (HPA) axis, which gets activated when a person goes through any form of stress, causing cortisol release from the adrenal glands.
  Surprisingly, the skin itself has its own peripheral form of the HPA axis capable of producing different hormones, including cortisol, CRH, and ACTH, which control processes like

inflammation, pigmentation, and epidermal barrier homeostasis. Nevertheless, hormonal imbalance can lead to several skin problems[14].

- Role of the Immune System-
  The immune system is an important mediator within the skin-brain connection, since it is responsible for the communication between psychological stress and the inflammatory response. In other words, the skin has immune cells like Langerhans, mast, and keratinocytes, which react to external and internal stimuli.
  In case of exposure to stress, the release of neuropeptides triggers an immune cell response and releases pro-inflammatory cytokines. This type of inflammation is called neurogenic inflammation, which leads to the formation of skin diseases like acne, psoriasis, and atopic dermatitis[15].
- Neurotransmitters Involved
  Neurotransmitters are critical biochemical factors involved in skin-brain communication, contributing to both physiological and psychological effects.
  - Serotonin: Involves the control of mood, melanin content, and tissue regeneration. It is also responsible for the maintenance of skin hydration and barrier function.
  - Dopamine: Participates in immune regulation and antioxidant defense. It is crucial for the maintenance of cellular equilibrium in the skin.
  - Cortisol: Called the major stress hormone, it impacts collagen production, skin elasticity, and inflammation reactions. Elevated cortisol secretion is linked with premature skin aging and poor tissue repair.
  - The availability of neurotransmitters in the skin emphasizes its neuroactivity and facilitates the creation of specific neurocosmetics [16].
  - Mechanism of Stress Affecting Skin-
    Stress has a great impact on the condition of the skin via several different pathways. First of all, when stress occurs, the brain triggers HPA axis, resulting in the release of cortisone and other stress hormones.
    Increased levels of cortisone cause disruption of the function of skin barrier due to reduced lipid content and increased TEWL. Moreover, stress causes inflammation and stimulation of mast cells, which worsens the overall state of the skin.
    Besides, stress leads to increased sebaceous glands activity and the development of acne. Finally, stress slows down the process of wound healing and accelerates the degradation of collagen and elastin. As discussed above, emotional and psychological issues are tightly associated with skin physiology[17][18].

III.PSYCHODERMATOLOGY AND SKIN DISORDERS

- Link Between Mental Health and Skin-
  Psychodermatology is a medical specialty concerned with the interrelationship between psychological issues and the health of skin. The skin and brain have a close relationship due to their common embryological development and constant biochemical interactions. Emotions, including stress, anxiety, and depression, may have direct effects on skin function, just like skin disease can impact a person's psychological state.
  The interplay between psychological problems and skin diseases establishes a vicious circle in which both elements feed off one another and aggravate each other's negative consequences [19].
- Skin Disorders Associated with Psychological Factors
  - Acne-Acne is one of the most prevalent skin disorders that are affected by stress-related factors. Stress causes an elevated level of cortisone hormones that promote sebaceous secretion, leading to the excessive secretion of sebum. The secretion of sebum provides favorable conditions for bacteria multiplication and inflammation, hence worsening acne condition. Moreover, emotional stress may cause delays in the healing process and increase pigmentation [20].

- Psoriasis-Psoriasis is a chronic skin condition characterized by inflammation. Psoriasis has been found to be exacerbated by stress through the stimulation of the immune system and release of cytokines that stimulate inflammatory processes. Patients diagnosed with psoriasis suffer from emotional stress because of the manifestation of their condition, which makes them prone to frequent flare-ups of the illness [19].
- Atopic Dermatitis-Atopic dermatitis (eczema) is yet another illness associated with psychological well-being. Psychological distress and stress can affect the barrier function of the skin and trigger more frequent scratching, causing further deterioration of the skin. Scratching and itching are known to be a vicious cycle that affects both the physical and psychological aspects of the illness [21].
- Effect of Stress, Anxiety, and Depression
  The effects of stress, anxiety, and depression are important elements in the development and evolution of certain skin diseases. Stress triggers HPA activation, leading to increased cortisol secretion and contributing to impairment of the skin barrier, inflammation, and premature aging.Stress and depressive reactions might affect the immune system as well as impair skin healing. Furthermore, patients who suffer from such mental issues may indulge in activities like picking at their skin or skipping skin care procedures.

In summary, the link between mental and skin health suggests the necessity to take an integrative approach to addressing patients' needs [19][20][21].

IV.NEUROCOSMECEUTICALS:- CONCEPT AND CLASSIFICATION

- Definition and Characteristics-

Neurocosmeceuticals are a new generation of cosmetic products, which are intended to affect the nervous system of the skin for improved physiological functioning and sensory sensations. The difference between neurocosmeceuticals and ordinary cosmetics lies in the fact that neurocosmeceuticals act directly on the nerves of the skin and control its reaction to external stimuli.These products can be easily recognized from their ability to affect the neurochemical messengers, create feelings of comfort on the skin, and induce sensations of well-being [22].

- Classification of Neurocosmeceuticals-
  Neurocosmeceuticals may be generally categorized depending on their mode of function as well as their mode of action:
  - Anti-Stress Ingredients-This class of neurocosmeceuticals acts to alleviate the effects of stress on the skin by balancing the level of cortisol and increasing the skin’s barrier integrity. Anti-stress ingredients are effective in alleviating stress-related inflammation, dehydration, and aging [23].
  - Mood-Boosting Ingredients-
    The use of neurocosmetics that boost mood involves sensory receptor activation and enhances relaxation and emotional well-being. Such ingredients could affect neurotransmitters or deliver aromatherapy benefits, thus improving the overall experience of using the product. Such mood-boosting ingredients can be found in neurocosmetics for soothing applications [22].
  - Anti-inflammatory neuroactives-
    Anti-inflammatory neuroactives act on neurogenic inflammation through modulation of the release of neuropeptides and inflammatory agents. These ingredients play an important role in relieving redness and irritation in the skin. Anti-inflammatory neuroactives have been utilized extensively in treating acne, rosacea, and eczema [24].

- Neurocosmetic Active Ingredients-
  - Adaptogens-Adaptogens refer to natural compounds that enhance the body's resistance to stress and aid in restoring physiological equilibrium. Adaptogens in neurocosmetics increase the skin's adaptability to both external and internal stress conditions. Among them are the Withania somnifera and Rhodiola rosea plants, which have calming and antioxidant effects [23].
  - Peptides-Peptides are chain molecules of amino acids that function like neurotransmitters. Certain neuropeptides in neurocosmetics inhibit the contraction of muscles, thus preventing wrinkle formation on the skin surface. Peptides are also important in repairing and maintaining skin structure [24].
  - Extracts of Plants-Plant extracts are extensively used in neurocosmetics because of their wide range of uses. Chamomile, green tea, and lavender have antiseptic, antioxidant, and calming actions. Some plant extracts are known for their neuromodulation effect, which contributes to their relaxing effect and helps improve the condition of the skin [22].

V.MECHANISM OF ACTION NEUROCOSMECEUTICALS

- Interaction with Cutaneous Nerve Endings
  The mechanism of action of neurocosmeceuticals is mainly through interaction with nerves within the skin tissue, specifically the epidermis and dermis layers. There are numerous sensory neurons within the skin that can sense various external stimuli, such as pressure, temperature, and chemicals. These sensory neurons produce peptides like substance P, which regulate vasodilatation and inflammation.
  Neurocosmetic active ingredients act on the above neural responses, providing a sensation of reduced irritation and discomfort [25].
- Pathway Modulation of Neurotransmitters
  In addition to these effects, neurocosmeceuticals have the ability to affect neurotransmitter pathways within the skin. The effects of peptides or other botanical actives could be similar to those of neurotransmitters like serotonin and dopamine.Modulation of these pathways leads to restoration of skin balance, minimization of stress-related reactions, and cell healing. This pathway modulation is extremely effective when dealing with issues related to neurogenic inflammation and sensitivities [26].
- Regulation of Hormone Signaling Pathways
  The hormone signaling pathway is important for skin biology. In particular, neurocosmeceuticals can regulate hormonal signaling pathways by blocking the effects of cortisol in the skin.Some biologically active substances can modulate the concentrations of cortisol, which enhances the adaptability of the skin to environmental stimuli. Consequently, this results in improved skin homeostasis without inducing any stress-related skin abnormalities, such as dryness, inflammation, and accelerated aging [25].
- Enhancing the Skin Barrier's Functionality
  The other crucial function of neurocosmeceuticals is improving the barrier functionality of the skin. Environmental conditions and stress can affect the barrier by limiting lipid production and increasing water loss through the epidermis.Neurocosmetic compounds assist in restoring the skin barrier by stimulating keratinocyte differentiation and lipid generation, thus enhancing skin hydration, lowering skin sensitivity, and shielding it from external damage [26].
- Anti-Inflammatory Activities
  The neurocosmeceutical ingredients display considerable anti-inflammatory activities due to their ability to interfere with the neurogenic inflammation process. These ingredients inhibit the secretion of pro-inflammatory cytokines and neuropeptides, which limits redness, irritations, and discomforts.

Ingredients such as peptides and plant-based compounds aid in calming the skin and modulating immune responses. The anti-inflammatory activity is especially important for skin disorders [25][26].

Stress activates the hypothalamic–pituitary–adrenal (HPA) axis, resulting in the release of cortisol and other stress hormones. Increased cortisol levels lead to inflammation, disruption of skin barrier function, and various skin disorders.The mechanism of stress-induced activation of the HPA axis and its effects on the skin are illustrated in Figure 2.

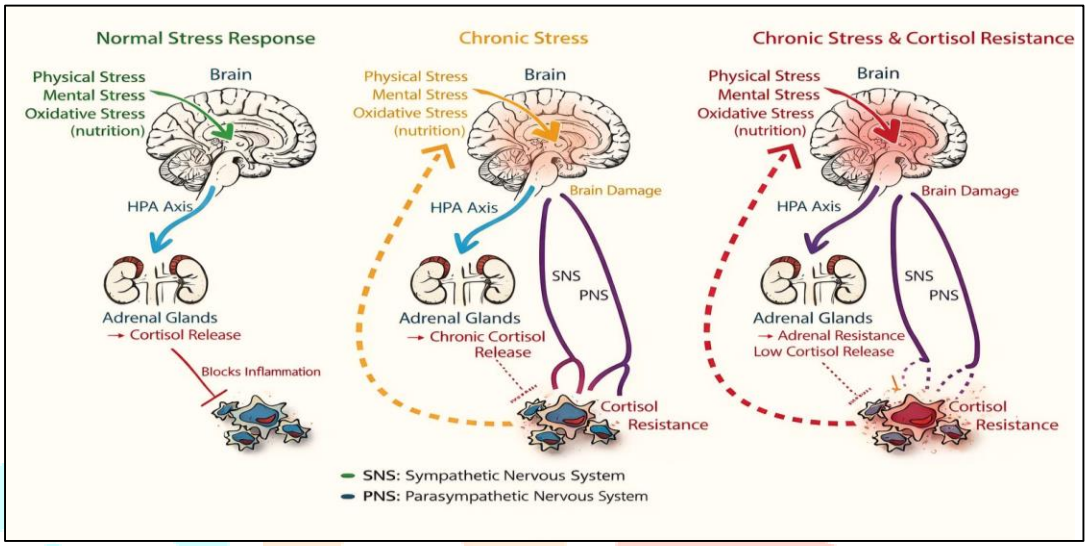

Figure 2: Stress-induced activation of the HPA axis leading to cortisol release, inflammation, and disruption of skin homeostasis.

Source – Adapted from Vashist et al.2014[50].

Activation of the HPA axis results in elevated cortisol levels, which impair skin barrier function, increase inflammatory responses, and contribute to conditions such as acne and premature aging.

VI.FORMULATION STRATEGIES OF NEUROCOSMECEUTICAL

Types of formulations

The efficacy of neurocosmeceuticals is highly dependent on the formulation used since the delivery, stability, and bioavailability of the active substances vary according to the type of product.

- Creams-
  Creams are one of the most common formulations owing to its oil-to-water ratio which helps in hydration as well as delivering lipophilic as well as hydrophilic neuroactive agents. It is recommended for dry and sensitive skin types [27].
- Gels-
  These light-weight and non-greasy preparations have a cooling property and can deliver the active substances efficiently without causing skin irritation [28].
- Serums-
  Serums are concentrated products meant to apply active substances in an efficient way. Being composed of molecules with lower molecular weight and having a liquid texture allows serums to better penetrate the skin and become extremely beneficial in delivering neuroactive compounds like peptides and antioxidants [29].
- Transdermal Systems-
  Transdermal systems are drug delivery systems such as patches and other topical carriers that allow the continuous delivery of neuroactive substances [30].
- Novel Delivery System-

For improving the efficiency of neurocosmeceuticals, modern delivery systems are often applied:

- Liposomes-
  Liposomes are vesicles based on phospholipids. These encapsulated structures enable better penetration of active ingredients to more depths of the skin. Liposomes are stable and do not cause irritation of the skin, thus, making them ideal for treating sensitive skin [31].
- Nanoparticles-
  Being extremely small structures, nanoparticles make a delivery system effective. Nanoparticles enable a targeted delivery of active ingredients [28].
- Microemulsions-
  Microemulsions are thermodynamically stable formulations that improve the solubility and penetration of the active agents. These contribute towards improving skin absorption [29].
- Stability and Permeability Concerns-
  The formulation of neurocosmeceuticals necessitates an understanding of stability and permeability to obtain the most effective formula. For example, peptides and plant extracts may be vulnerable to environmental factors like light and oxidation. This means that there is a need for proper stabilizers and containers.

Another essential parameter is permeability, since efficient neuroactive compound delivery is determined by its capacity to diffuse through the stratum corneum. The utilization of technologies like nano-encapsulation, application of penetration enhancers, and proper formulation of skin pH are crucial in this aspect.

In general, an adequate formulation process guarantees maximum efficacy, safety, and customer satisfaction for neurocosmeceuticals [30] [31].

VII.EVALUATION AND CHARACTERIZATION OF NEUROCOSMECEUTICALS

- Physicochemical properties -
  Evaluation of physicochemical properties plays an important role in the determination of quality, stability, and performance of the neurocosmeceutical formulation. pH, viscosity, spreadability, particle size, and zeta potential play an important role in determining the physicochemical properties.
  Conducting studies on stability in varying environmental conditions, including temperature, humidity, and light, also becomes necessary for shelf life evaluation. The maintenance of good physicochemical properties becomes imperative to achieve consistency and efficiency [32].
- In Vitro Experiments (Diffusion Experiments)
  In vitro diffusion experiments are conducted to study the release and penetration of pharmacologically active substances through the skin. These include methods such as the use of Franz diffusion cells, which are used to model drug diffusion through natural or artificial membranes.The main objective of conducting these experiments is to measure the efficiency of neurocosmeceuticals' penetration. This approach allows for the adjustment of formulation conditions, which is necessary at the initial stage of developing new drugs [33].
- In Vivo Trials-
  These trials require the application of the formulations to animal models or human test subjects to determine their biological behavior. Information is gained about how effective the product can be concerning skin absorption, its hydrating properties, elasticity, and anti-aging qualities.If the product in question is a neurocosmeceutical, additional sensory reactions will be measured, such as any soothing or relaxing properties that the compound has [34].
- Clinical Trials-
  Clinical trials are extremely important for the validation of safety and effectiveness of neurocosmeceuticals. These tests are carried out on human participants to determine factors like decrease in wrinkles, increase in skin moisture levels, and decreased inflammation and sensitivity.State-of-the-art non-invasive methods, including corneometry, tewametry, and

imaging technology, can be employed to collect objective information. Clinical studies also help in establishing facts about the product and adhering to regulation [35].

- Safety and Toxicity-
  The safety assessment process constitutes an important part of the neurocosmeceutical development process. Toxicity assays include skin irritation, sensitization, and allergy assays to determine the safety of the product for its intended use.Newer strategies involve the adoption of alternative in vitro techniques to limit the number of animal trials required. Further, any new means of delivery such as nanoparticles should be carefully tested for their safety in the long run.It is vital that neurocosmetic products are safe and have minimum toxic properties to gain consumer confidence [32][35].

VIII.REGULATORY ASPECTS OF NEUROCOSMECEUTICAL

- Difference between cosmetic and pharmaceutical regulations-
  Neurocosmeceuticals can be said to be in between cosmetics and medicines, which makes their classification difficult. According to the Food and Drug Administration Act, cosmetics are any product that cleanses, beautifies, enhances one's appearance, or modifies the body without altering its functions or structure. On the other hand, medicines or drugs are meant to diagnose, cure, mitigate, or prevent any illness.Unlike cosmetics, neurocosmeceuticals may have some physiological activities due to their role in modulating neural pathways and skin physiology. Neurocosmeceuticals may not necessarily fall under the category of medicines because of their cosmetic nature and lack of therapeutic claims, which is critical in the formulation process and regulations [36].
- Worldwide Guidelines (USA, Europe, India)
  Cosmetic products have different regulations around the world, yet each stresses safety, labeling, and quality.
- USA: Cosmetics are regulated in the USA according to the Federal Food, Drug, and Cosmetic Act by the FDA. Cosmetics cannot be approved before entering the market, yet they have to be safe to use and appropriately labeled. However, if the item modifies skin functioning, it falls into the category of a drug, which means a more rigid regulation [37].
- Europe: The European Union regulates cosmetics according to Regulation (EC) No. 1223/2009 that entails detailed safety assessment, restrictions concerning the usage of certain ingredients and Product Information Files (PIF). Europe possesses an elaborate regulatory process, such as obligatory notifications using the Cosmetic Products Notification Portal (CPNP) [38].
- India: The regulation of cosmetics in India is based on the Drugs and Cosmetics Act, 1940, and Rules, 2020. The act is administered by the Central Drugs Standard Control Organization. Cosmetics should conform to safety standards, labeling regulations, and licensing procedures. Nevertheless, advanced cosmetics such as neurocosmeceuticals are not clearly classified in India compared to international classification systems [39].
- Classification Issues-
  The major issue in classifying neurocosmeceuticals is their dual purpose. Even though they are considered cosmetics, their modes of action frequently include biochemical or neurological processes. It is difficult to classify such products due to their ability to deliver physiological and neurological effects, such as stress relief, enhanced mood, and anti-aging benefits.Another issue with classifying cosmeceuticals and neurocosmeceuticals is the absence of an official definition that would help establish regulatory practices globally. Moreover, the development of new technologies and products based on nanoparticles and bioactive peptides requires a reevaluation of safety criteria.These issues demonstrate the necessity to update existing regulatory policies in order to accommodate advances in cosmetic technologies [36][37][38][39].

IX.MARKET TRENDS AND COMMERCIAL PRODUCTS

- Growth of Neurocosmetics Industry -
  Recent years have witnessed an expansion in the neurocosmetics sector as a result of the emergence of neuroscience as a discipline that can be combined with cosmetology. Global sales in neurocosmetics continue to grow owing to increased customer knowledge about the link between mental well-being and skin care. It was predicted that the future growth rates of sales for such products would be around 8-9% per year [40][41].In addition, the progress in research and development allows adding neuroactive substances to cosmetics. Consequently, there will be a shift from conventional cosmetics to more effective and sophisticated formulas [40].
- Consumer Interest in "Emotional Skincare"-
  One of the emerging trends in the contemporary cosmetic industry is consumer interest in "emotional skincare," a skincare approach focused on the relation between one's emotional state and skin health. In addition to seeking cosmetics to achieve a desired look, people are now interested in products that can reduce stress, bring relaxation, and boost mood.This trend may be regarded as a sign of the growing popularity of wellness-inspired beauty regimes where skincare plays an integral role. As revealed by research findings and industry statistics, skin problems linked to stress, such as acne, irritability, and early signs of aging, motivate consumers to use beauty products addressing both psychological and dermatological issues [42].In addition, the importance of sensorial properties such as scent, feel, and application ritual is highlighted [41][42].
- Examples of Available Commercial Products
  Many commercial products that are available in the market today are based on the concept of neurocosmeceuticals.
  - Adaptogen creams: These cream products include components like ashwagandha and reishi that prevent skin damage caused by stress and increase skin resistance [43].
  - Neuropeptide serums: These serums are formulated to relax facial muscles and prevent wrinkles by regulating neurotransmitters [43].
  - Herbal calming products: Some products include lavender, chamomile, and green tea extract to soothe the skin and promote relaxation [42].
  - Skin care products for mood improvement: Specific products have been formulated to affect emotions by decreasing cortisol levels [41].

These commercially available products show how neurocosmetology ideas are being applied in the beauty industry, emphasizing the importance of the integration of skin and brain health solutions [40–43].

X.CHALLENGES AND LIMITATIONS

- Scientific Validation Issues
  One of the key obstacles in the field of neurocosmeceuticals is the paucity of scientific evidence that substantiates their effectiveness. Although several formulations assert their capability to impact neurochemical pathways, the connection between the external application and any observable changes in neurophysiology has yet to be proven adequately. Clearly, there is an urgent need for conducting adequate experimentation and research to establish the truth [44].
- Absence of Standardized Testing
  Another major constraint that hinders the growth of this field is the lack of standardized tests to determine the impact of such products on neurological and psychological states. Unlike drug testing, there are no standard procedures to test the impacts of neurocosmeceuticals on the brain. Differences in testing processes result in varied outcomes from one test to another, rendering results unverifiable [45].
- Regulatory Uncertainty
  Due to the fact that neurocosmeceutical products are neither cosmetics nor medicines but contain some sort of functionality, they have ambiguous regulatory status, which results in inconsistencies

in the methods of evaluation and certification across different regions. This poses problems for manufacturers in compliance and international marketing of neurocosmeceuticals [46].

- Formulation Stability
  The next significant issue is related to the sensitivity to various environmental conditions (heat, light, oxidation), as well as to degradation during the period after packaging. The challenge is not only to formulate a stable product but one that still possesses neuroactivity [45].

XI.FUTURE PERSPECTIVE

AI-Based Personalized Skincare

- AI in Skincare-
  The use of artificial intelligence in skincare is projected to bring about a paradigm shift in neurocosmeceuticals through personalized formulation design. The application of artificial intelligence can help develop formulations that consider personal skin health, habits, and levels of stress to provide a tailored solution for better results and user satisfaction [47].
- Advancements in Drug Delivery System-
  There have been considerable advances in the area of drug delivery system, including the utilization of nanocarriers, liposomes, and transdermal delivery, which would improve the efficacy of neurocosmeceuticals [48].
- Neurocosmetics and Neuroscience-
  Further development of neurocosmetics will require increased integration with neuroscience studies. An enhanced knowledge of the mechanisms of skin-brain communications, neurotransmitter functions, and neurogenic inflammation can help create even more efficient products. This cross-disciplinary direction can provide the additional scientific grounds for the formulation of neurocosmeceuticals [44][47].
- Management of Psychodermatological Disorders-
  Neurocosmeceuticals have significant potential to be used for the management of various psychodermatological disorders, including stress-acne, psoriasis, and atopic dermatitis. Neurocosmetics can help address both psychological factors and their impact on skin health. Even though there is still much work to be done in this area, promising results are obtained [46][48].

XII.CONCLUSION

Neurocosmeceuticals represent a significant and innovative advancement in contemporary cosmetic science, characterized by the integration of dermatology, neuroscience, and pharmacological principles to target the complex interactions within the skin–brain axis. By recognizing the skin as a neuro-immuno-endocrine organ, these formulations aim to address the underlying mechanisms through which psychological stress influences skin physiology. The modulation of neuroendocrine pathways, particularly the hypothalamic–pituitary–adrenal (HPA) axis, plays a crucial role in mitigating stress-induced effects such as inflammation, oxidative damage, impaired barrier function, and premature aging.

The incorporation of bioactive ingredients, including peptides, adaptogens, antioxidants, and plant-derived compounds, enhances the therapeutic potential of neurocosmeceuticals by regulating neurotransmitter activity, reducing neurogenic inflammation, and promoting overall skin homeostasis. Furthermore, recent advancements in formulation and delivery technologies, such as liposomes, nanoparticles, and transdermal systems, have improved the stability, permeability, and targeted delivery of these active agents, thereby increasing their efficacy and consumer acceptability.

Despite these promising developments, the field faces several critical challenges. Limited scientific validation, absence of standardized evaluation protocols, formulation instability, and regulatory ambiguity continue to hinder widespread clinical acceptance and commercialization. Addressing these limitations requires robust experimental research, well-structured clinical trials, and the establishment of globally harmonized regulatory frameworks.

Looking forward, the integration of artificial intelligence and personalized skincare approaches is expected to further enhance the effectiveness and precision of neurocosmeceutical formulations. In

conclusion, neurocosmeceuticals offer a comprehensive and multidisciplinary approach to skincare, with the potential to redefine conventional cosmetic practices by addressing both physiological and psychological determinants of skin health, ultimately contributing to improved dermatological outcomes and overall well-being.

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