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HERBAL DRUG LOADED NANOGEL FOR EFFECTIVE TREATMENT OF SKIN DISORDERS

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ABSTRACT: Since ancient times, plants have been used for medicinal purposes for their various therapeutic potentials and safest to modern allopathic medicines. Regularly phytochemicals are proving to be modern medicine with novel drug delivery systems by treating different diseases and disorders. Phytochemical compounds need improvement of efficacy and patient's compatibility to deliver in various diseases, e.g., high blood pressure, microbial, coronary heart disease, cancers, diabetes, inflammation, etc., also require a rational approach. Nanotechnology is a promising drug delivery approach for targeted or site-specific phytoconstituent delivery. Especially, Nanogels are the most rational approach for targeting skin diseases and enhancing bioavailability. Phytoconstituents or plant extract-loaded nanogels have been reported in *in-vitro* and *in-vivo* activities for different skin disorders like aging, acne, skin infection, *etc*. Nanogels, as a novel drug delivery system, may reduce toxicity and improve the bioavailability of the incorporated drug. The present review is focused on various phytomedicines that have been used in treating skin aging and acne, nanogel formulations prepared, and the effectiveness of both phytochemicals and nanotechnology for skin disorders treatment.

INTRODUCTION: Skin is the prime exposed and visible organ of individuals. It defends internal organs from surrounding and dehydration [1, 2]. There are assured skin situations, e.g., burns and another considerable failure of the superficial skin layer (epidermis), which works as the barricade that stops the skin from deterioration and microbial invasion and maintains equilibrium in the body's liquid levels. In such conditions, *Acne vulgaris* and other microbial infections skin get damaged. In aging, skin gets less elastic, wrinkled, lax, and rough-textured appearance.

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Hence, aging, *Acne vulgaris*, and other microbial infections can drastically impact human health and social life. Different diseases, like *Acne vulgaris*, eczema, rosacea, herpes zoster, and psoriasis, can cause harm to the skin; however, infections are the major cause of skin damage [3]. *Acne vulgaris* is a transmittable disease and is identified by various areas of seborrhea (scaly red skin), papules (pinheads), comedones (whiteheads) and blackheads, nodules (large papules), and sometimes piples (scarring) [4].

Usually, severe acne is inflammatory though it can be non-inflammatory too. In acne, the skin modifies because of alteration in pilosebaceous unit skin structures comprising hair follicles and their linked sebaceous glands. Usually, androgen stimulation is responsible for these modifications [5] occurs during puberty more often in adolescence, regardless of sex. Generally, acne appears on the

face, back or upper chest, where greater numbers of oil glands are found [6]. Aging is also a skin-related disorder, the most complex biological event processed under intrinsic and extrinsic factors.

Intrinsic factors, also known as endogenous factors, include cellular metabolism, genetics, metabolic processes, and hormone; extrinsic factors, known as exogenous factors, include pollution, chronic light exposure, ionizing radiation, toxins, and chemicals [7]. These factors cumulatively work and result in physiological, progressive, and structural changes in different skin layers, especially in sunburned skin areas; skin appears tanned, then changes in internal layers [8, 9].

Thin and atrophic skin shows intrinsically dry aged skin and fine wrinkles, while typically thickened epidermis-comprised skin shows deep wrinkles, dullness, mottled discoloration, laxity, and roughness [10].

A steady loss of skin elasticity directs towards another aging phenomenon known as sagging [11]. Nanotechnology is an outstanding strategy for fast healing skin diseases due to increased drug loading capacity and manipulating various phases of healing [12].

Since, last 2 centuries, the craze for plant extracts for healing skin disorders has been increasing continuously because of the occurrence of active agents in plant extracts [13].

However, plant extracts and isolated compounds have many problems related to their pharmacokinetics *e.g.* absorption, bioavailability *etc*. Herbal-originated medicines have no or low side effects, and high efficiency makes them universally acceptable and elegant to research [14].

World's 80% population accepts herbal drugs or constituents for the treatment of skin-related diseases and other disorders [15]. Different studies have been performed on various plant extracts to study the pharmacological activity of plant constituents on various diseases.

The global herbal medicine market is projected to grow from USD 230.03 billion in 2021 to USD 430.05 billion in 2028 at a CAGR of 11.32% [16]. Different types of Nanocarriers of various herbal drugs have collected noteworthy identification for their potential and characteristic features in several fields of human activity [17].

The medicinal potential of natural drugs can be enhanced by using a marvelous combination of nanotechnology and natural drugs as novel drug delivery systems [18].

There are many problems with these plant-oriented drugs *e.g.*, the acceptability of these compounds by patients and dose frequency; these problems can be improved by using a correct approach that may support the sustained release delivery of active plant constituents. Novel drug delivery systems assist in attaining the essential therapeutic effects with reduced adverse effects and improve the bioavailability of herbal constituents [19].

Skin Diseases: Acne develops as an outcome of follicles blockage, keratin plug formation, hyperkeratinization, and sebum (microcomedo), also a result of bacterial overgrowth with inflammation in the pilosebaceous units. The hormone level of the body increases, sebaceous glands are enlarged, and sebum production is generally increased it occurs at the time of puberty.

Epithelial cells of follicles differentiate abnormally, tightening adhesion between cells and shedding less. Further, these events lead to the formation of microcomedones or hyperkeratotic plugs, which can expand to appear as a non-inflammatory open comedo (blackhead) or closed comedo [20]. Also, comedones can occur due to clogging sebaceous glands with sebum, dead skin cells, and naturally occurring oil [21].

The overall conclusion is that the hyperproduction of Androgens is the main contributory factor for acne, which starts the series of events it includes sebum production, hyperkeratinization, keratin plug formation, dead cell aggregation, and finally, bacterial growth leading to the comedones development [22].

Alterations in natural skin flora are related to sebum production due to androgen. Polycystic ovarian syndrome and endocrine tumors are those diseases that elevate the androgen level in the body, further leading to the development of *Acne vulgaris* [23].

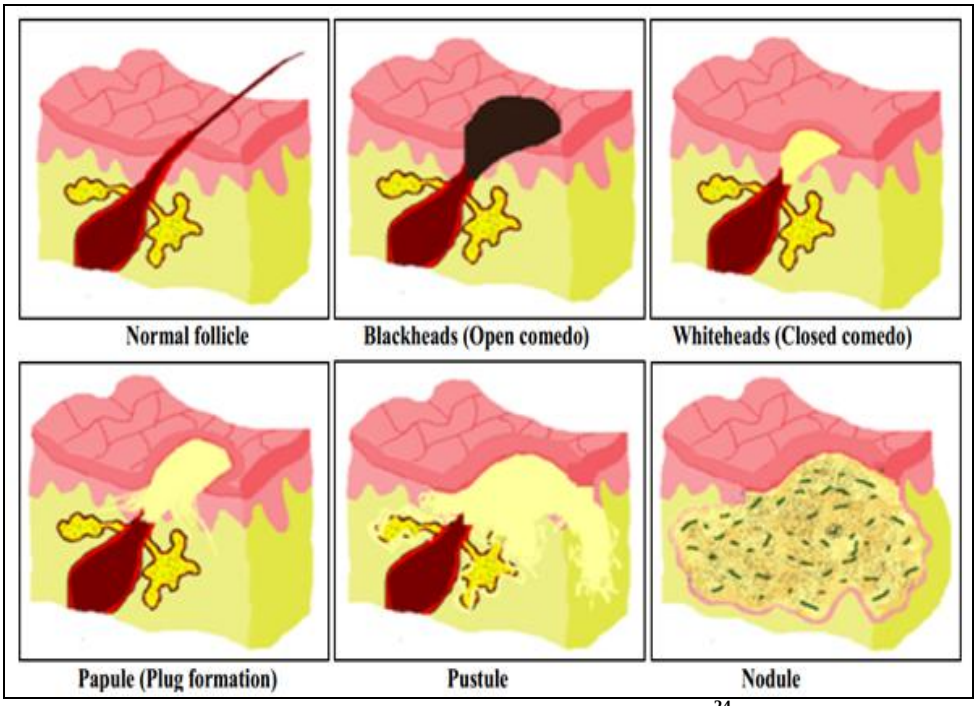

FIG. 1: DIFFERENT TYPES OF ACNE [24]

Aging can be defined as fine or deep wrinkles, dull skin, mottled discoloration of skin, laxity, and roughness on the skin. Aging can be of two types based on distinct processes. First is sun-exposed skin, also called photoaging and sun-protected skin, also called intrinsic or chronological aging, but both types have general and exclusive demonstration and molecular mechanisms. Intrinsic aging is usually linked with increased dry skin (xerosis), laxity, and fine rhytids. Photoaging shares the above-described features but also demonstrates mottled pigmentation, telangiectasias, deeper rhytids, and elevated growth rate of malignant neoplasms [25].

Histologically, photoaging expresses irregular thinning of the epidermis with thickening of the granular layer and more compact corneal layer, dermal ECM loss of collagen and elastin, and improved dermal inflammation [26]. These discoveries related to histology are associated with enhanced gene expression of matrix metalloproteinases and suppressed gene expression of ECM components, principally elastin and collagen [27]. These alterations are located in several photoaging models and used as markers in various therapeutic and mechanistic studies [28]. Various models are available that time to elucidate the molecular basis for skin aging, including the theory of cellular senescence, reduces in cellular DNA repair ability and failure of telomeres, oxidative stress, point mutations of extranuclear mitochondrial DNA, increased frequency of chromosomal abnormalities, reduced sugar, single-gene mutations, chronic inflammation and so on [29]. Several researchers suggested that most effects are caused by extrinsic factors, while only 3% of aging is caused by intrinsic background [30].

The Plant Potential against Skin Aging and Acne: Acne-causing bacteria become resistant to the drugs if used for a long time. Due to low toxicity and side effects, herbal medicine is becoming popular compared to allopathic [24].

The natural system of medicine focuses on the entire body and treats the root cause of acne. In contrast, allopathic medicine focus only **on** Plants, and their natural constituents are renowned for possessing antioxidant potentials, such as vitamins, flavonoids, and flavones that assist in treating and preventing ROS-linked chronic situations. These supplements have antagonistic effects against the degenerative and inflammatory procedures in the body and demonstrate favorable effects on the digestive and immune systems, therefore developing the quality of life [32]. For a long use of an antibacterial for acne, acne-causing bacteria become resistant, so there is a continuous need to launch newer drugs. Herbal drugs have become

popular and attractive due to lower side effects and toxicity than allopathic medicines [33]. Naturally originated drugs can treat the root cause of acne.

In contrast, allopathic medicine only gives symptomatic relief, e.g., blemishes linked to inflammation control, reduction of redness, *etc.* [34]. The negligible adverse effects of herbal drugs make them the first choice for treating acne. Herbal therapies will increase the interest of researchers, cosmeticians, dermatologists, academicians, and industrialists in treating acne in the forthcoming years. Herbs as medicine for acne treatment can be administered either internally or externally or with both. The most preferred administration selection is topical application of herbs because of ease of application, whereas administered internally may cause an unpleasant or bitter taste. Herbs are used as the main component of many cosmetic and antiacne preparations because of their efficacy and safety.

Herbal medicine can be used alone or synthetic drugs to treat skin diseases. More prominently, other than being used as preventive or treatment medication, it might be given together with synthetic drugs to prevent side effects or to produce a synergetic effect. Herbal drugs are used accompanied by other methods or single to treat *acne vulgaris*. There is a long list of medicinal plants having antiacne, anti-aging, anti-inflammation, and antibacterial activities, used in different ways of treatment, some of them described below:

Achyranthes aspera: Belonging to the family *Amaranthaceae,* commonly known as Apamarga or prickly chaff flower. Traditionally it is used to manage *Acne vulgaris*, boils, skin eruptions, and scabies, like many skin diseases. Leaves of apamarga were extracted in the form of Saponin, alkaloid, and non-alkaloid fractions. They found a massive inhibitory effect on the Epstein-Barr virus early antigen activation in Raji cells. But the non-alkaloid fraction possessed the most inhibitory activity (96.9%; 60% viability), having mainly non-polar compounds.

In another study, total methanolic extract was evident as an anti-carcinogenic effect with 76% inhibition. Different studies suggested that plants possess abortifacient and contraceptive activities because of their estrogenic potency [35].

Allium cepa: Belonging to the family *Amaryllidaceae,* commonly known as Onion. A gel containing onion extract has been investigated in the case of seborrheic keratosis to enhance the appearance of the scar in 4, 6, or 10 weeks of usage by improving softness, redness, and texture at excision. During another antimicrobial and antifungal study of *A. cepa* with *A. sativum* extract was found to be active against *Candida albicans* and other *Candida* species and *Malassezia furfur* as well as few strains of dermatophytes and *Acne vulgaris* microbes. The study concluded that *A. cepa* and *A. sativum* can be promising remedies for fungal and bacterial-oriented infections [36].

***Aloe barbadensis* Miller:** Belonging to the family *Asphodelaceae,* commonly known as Gritkumari. *Aloe vera* leaf gel can be administered locally to treat various skin diseases *e.g.*, dermatitis, seborrheic, Vulgaris, psoriasis, skin burns, genital herpes, and *acne vulgaris.* It possessed Anti-acne, antioxidant, antimicrobial; Anti-inflammatory effect proved *in-vivo; the* responsible compounds are Aloin and emodin [37].

***Amaranthus hypochondriacus* Linn and *A. cruentus* Linn:** Belonging to the family *Amaranthaceae,* usually called "Prince-of-Wales Feather" are native to Mexico and China. Seeds and leaves of amaranthus are used successfully as an astringent and also formulate a good wash for skin complications ranging from acne and eczema to psoriasis [38]. The main constituents are saponins.

***Arctium lappa* Linn:** Belonging to the family *Asteraceae* is usually known as burdock, thorny burr, etc. The leaves and roots of burdock are generally used for treating acne-like chronic skin problems [39]. It contains various constituents, e.g., sesquiterpene lactone (arctiopicrin), lignan (arctigenin), fructosan (inulin), and mucilage (xylocan) [40].

***Arnica montana*:** Belonging to the family *Asteraceae,* common names are leopard's bane, and mountain tobacco. Arnica is a mountain-growing herb found in southern Russia to Europe [41]. Dried *Arnica* flower heads are valuable to treat acne, sprains, muscle aches, bruises, and as a common

topical counterirritant [42]. Arnica contains various phytoconstituents glycosides flavonoid, sesquiterpene lactones (dihydrohelenalin, helenalin, arnicolides and the arnifolin) and about 0.3% of a volatile oil [43]. Helenalin and dihydrohelenalin esters are active principles obtained from arnica responsible [44] for its antioedema, antimicrobial and anti-inflammatory activities.

***Asparagus Officinalis*:** Belonging to the family *Liliaceae,* known as Shatavari or sparrow grass, commonly cultivated in Asia and Europe. Seeds and fleshy roots have been used for therapeutic purposes. Shatavari root holds numerous compounds *e.g.* fructo- oligosaccharides, bitter glycoside (officinal sins I and II), inulin, steroidal glycosides (asparagosides A to I) β-sitosterol, and asparagusic acid, yamogenin [45]. Since ancient times, extracts of Asparagus used to cleanse the face and acne form lesions as home remedies.

Azadirachta indica: Belonging to family *Meliaceae* commonly known as Neem. A study conducted for evaluation of antiacne potential, a formulation from herbal extracts was prepared, comprised of ethanol extract of *Azadirachta indica, Andrographis paniculata, G. glabra, Ocimum sanctum* and green tea and revealed that it possessed the antiacne potential. Also observed the formula was succeeding against Propionibacterium and *Staphylococcus epidermis* for antiacne [46]. Chemopreventive activity was evaluated in aqueous extract of *Azadirachta indica* leaves against murine skin carcinogenesis. In comparison to the control group skin tumors that enhance the expression of proliferating cell nuclear antigen were inhibited by aqueous extract, skin tumors exhibited high lipid Peroxidation [47].

***Betula alba* Linn:** Belonging to the family *Betulaceae,* commonly known as Birch, originated in India, Northern Europe, Northern U.S, and Canada. It is reported that tree bark has been applied effectively to treat eczema, psoriasis, acne, and similar chronic skin diseases [38]. Phenolic compounds are mainly occurring constituents, salicylic acid, and guaiacol; betulin, ylangene, terpenoids, betuloside and flavone, sakuranetin [40].

***Calendula officinalis*:** Belonging to family *Asteraceae,* the flower heads of Calendula have long been applied for treating different skin diseases, including assisting in healing and inflammation reduction [42]. The Calendula herb contains triterpenoids, flavonoids, *e.g.*, quercetin, saponins *e.g.,* arvenoside A), polysaccharides, and essential oils [48].

***Cannabis Sativa*:** It is the plant of *cannabaceae* family, the seed oil of *Cannabis sativusis* useful for the treatment of acne rosacea, eczema, dermatitis, seborrhoeic dermatitis, psoriasis, and lichen planus. The leaves powder is applied in dressing of wound and sore. *Cannabis sativus* extract is externally useful to relieve pain in itchy skin. The seed oil also useful to skin strength and makes it more resistant to fungal, bacterial and viral infections [49].

***Chelidonium majus*:** It is a plant of *Papaveraceae* family and a perennial herb. Geographically it is found in different reason of Asia and Europe. Sticky, acidic, orange juice exudes from the broken herb parts is applied for pimples treatment [38] unpleasant in odor**.** Isoquinoline alkaloids of proberberine benzophenanthrene and protopine type constituents are its main chemicals.

***Curcuma longa* Linn:** This plant belongs to *Zingiberaceae* family, commonly known as Turmeric basically dried rhizomes. Cultivate widely throughout India, Asia, China, and Tropical countries. It contains majorly curcuminoids, responsible for the yellow color, which curcumin constitutes 50-60%, essential oil (2-7%) with high bisatiolane derivatives [50]. Turmeric possesses extraordinary anti-inflammatory potential due to the presence of curcumin [51].

Echinacea Angustifolia* and *Echinacea Purpura: This plant belongs to the *Asteraceae* family; the *Echinacea Purpurea* extract evaluated against *P. acnes* involved in acne vulgaris. The study revealed that the Echinacea extract can completely reverse substantial secretion of several pro-inflammatory cytokines, *e.g.* IL-6 and IL-8, during cell culture model evaluation. Hence, this plant provides double advantages to acne patients. First is inhibition of the proliferation of organisms and bacteria-induced inflammation [52]. Echinacea can also treat various other skin complications, *e.g.*, skin wounds, psoriasis, burns, herpes ulcers, and hemorrhoids [53].

***Eucalyptus Globulus, E. Viminalis* and *E. Maculate*:** Belongs to the family *Myrtaceae*. 29 species of Eucalyptus were evaluated for antimicrobial activities in one study and *Eucalyptus globulus, E. viminalis* and *E. maculate* were found active against six strains of gram-positive bacteria including *P. acnes, Enterococcus faecalis, Bacillus cereus, S. aureus* and fungi *Trichophyton mentagrophytes* while no significant activity against gram-negative bacteria.

A component 8-desmethyl-eucalyptin found in *E. maculate* also reported potential against the microorganisms mentioned above. It is concluded that active principles of Eucalyptus extracts are responsible for the antimicrobials causing acne and Athlete's foot infection, as well as some fungal infections [54].

***Juglans nigra* Linn and *J. Regia* Linn:** These are the various species that belong to the family *Juglandaceae* known as walnuts are originated from India to East Asia, North and South America, and Southeast Europe. The walnut's hard upper cover and tree part is used to formulate an excellent wash and scrubs for various skin infections, including Acne vulgaris [38]. These plant extracts are rich sources of naphthalene derivatives, juglone tannins (elagitannin), quercitin, and flavonoids hyperoside [55].

Melaleuca Alternifolia: Belongs to **the** family *Myrtaceae*, a tree or long shrub known as a tea tree. Geographically it is distributed in Australia, the north coast of New South Wales. Essential oil of plant leave obtain by steam distillation is used for medicinal purposes [56]. Terpin-4-ol (40%) is the main constituent is evaluated for a range of organisms found effective against 27 out of the 32 strains of *P. acnes* [57].

Tea tree oil is a broad-spectrum compound against Gram-positive and Gram-negative bacteria and even *S. aureus* resistant to methicillin and yeasts such as *C. albicans in-vitro*. Monoterpenes involve in a mechanism of action which causes an interruption in the plasma membrane barrier. Tea tree oil possesses anti-inflammatory activities and monocyte activators. Topically tea tree oil has use as anti-acne potency in low concentrations with low side effects. It is efficient in osteomyelitis and chronic infectious wounds [58]. It has high penetration with non-irritating action on the skin.

***Rheum Officinale*:** Rheum belongs to **the** family *Polygonaceae* and other species are distributed to India, China and Southern Siberia. Rheum contains various constituents like calcium, potassium, and phosphorus (low amount). The anthraquinones present are rhein, emodin, chrysophanol [59] in rhubarb are useful to relieve the itchness and pain accompanying psoriasis as well as *Acne vulgaris* [38].

Rose: Numbers of rose species belong to the family *Rosaceae;* aqueous petal extracts are applied to the skin for daily care. Against acne and blackheads, rose water is also a potential tool [38]. Rose water contains mainly tannins pentagalloyl, pyrogallol, eugeniin, monoterpenoids- geraniol, eugenol, and rugosal and phenylethyl alcohol [40].

***Rosmarinus officinalis*:** *Rosmarinus officinalis* belongs to *Lamiaceae,* a household ornamental plant. It is generally used as a beverage drink, in cosmetics as well as flavoring food. The aqueous extract of *R. officinalis* has antioxidant potency, which is why effective against photodamage induced by UV radiations. Also, antibacterial activity was evaluated against *P. acne-causing bacteria and* reported noteworthy alteration in size and morphology of *P. acnes* in response to treatment [60].

***Saponaria officinalis*:** Belonging to the family *Caryophyllaceae* general name is soapwort, a perennial herbaceous plant grown in Northern Europe. Soapwort uses topically to treat psoriasis, acne, eczema, and boils [44]. This plant has steroidal saponins (saponoside D), which are water-soluble and occur in all parts and work as a surface-active agent as a cleaning aid.

***Thymus vulgaris* Linn:** Thyme belongs to the family *Lamiaceae* and are small, perennial plants grown in Asia and Europe. Various differences in leaf color, shape, and essential oil composition are found according to their geographical occurrence. The leaves are formulated as salves that use as a remedy for acne, cuts, burns, and rash in the area of the face, neck, throat, or forehead [38]. Thyme contains thymol acetate, carvacrol, p-cymene, thymol and apigenin [40].

***Urtica dioica*:** Belongs to family *Urticaceae* also known as *s*tinging nettle herb, consists of dried or fresh leaves or aerial parts. Its leaf and herb are rich in mineral salts *e.g*. calcium and potassium salts of silicic acid; amines-acetyl choline, phenolic ketones-acetophenone; histamine, betaine, choline, 5-HT, lecithin; β-sitosterol, tannins, flavonoids-quercitin, isoquercitin, rutin, kaempferol; volatile oil, vitamins A, B2, C, K, folic acid and pantothenic acid [61]. The alcoholic solution of distilled nettle is applied to treat acne traditionally [56].

Nanogel Mechanism in Treatment of Skin Disorder: There are several drug release mechanisms, including degradation of nanogel structure, simple diffusion, temperature and pH changes, counter ion displacement or induced due to external energy source [62] some are described below:

Thermosensitive & Volume Transition Mechanism: Thermosensitive polymer gel mechanism depends on the reversible volume change from collapse to swell via irregular volume change with temperature. Three patterns were observed as (1) Thermoswelling is shrunken-swollen of polymer with irregular volume change (2) Thermoshrinking is swollen- shrunken of polymer with irregular volume change (3) Convexo pattern is shrunken-swollen-shrunken with two irregular volume change. For intense N–isopropyl acrylamide is a polymer that efflux indomethacin drug by initially shrunken in gel volume with the temperature reaches above lower critical solution temperature (LST) [63] while N – isopropyl acrylamide – co – acrylamide polymer release 5 – fluorouracil drug at body temperature [64]. Superficially modified polyethylene used to formulate nanogels effectively applied for gene delivery systems [65]. Poly alkylene oxides containing nanogel's thermally trigerred volume can be increased 1 µm in nanogel size [66]. Nanogels of poly (N–isopropyl acrylamide) and chitosan, the lower critical solution temperature, could be altered by altering in the ratio of polymers and used in hyperthermic cancer treatments [67].

Photochemical Internalization & Photo isomerization: Nanogels containing photosensitive polymer produces nascent oxygen during photochemical excitation by light is reactive oxygen species cause oxidation of cellular wall components, which affects drug release into cytoplasm easily, or else inhibited by intracellular compartment [68]. In photoisomerization, the polymer of nanogels converts their configuration in the presence of light *e.g*., Cis-trans isomerization, E-Z configuration, etc. Nanogels having azo dextran as polymer E- configuration shows better aspirin release profile than Z- configuration of the azo group at 365 nm radiation [69].

Diffusion Mechanism: In this type of mechanism drug travels from high concentration to low concentration. Numerous nanomedicines have already been prepared that pursue a diffusion mechanism, is a simple procedure, *e.g.* polymeric micelles that have in clinical trail stage [70]. Stable hydrogel nanoparticles of Doxorubicin formulated using puronic block copolymer follows the diffusion mechanism for drug release.

PH Responsive Mechanism: Nanogel containing platinum nanoparticles at the acidic skin pH the reactive oxygen species scavenging on & off catalytic activity and protonation of crosslinked poly (2 – (N, N – diethylamino) methacrylate) core and PEG [71] when lower the pH the polymers methacrylic acid ethyl acrylate are insoluble, again on increasing of pH, acidic groups ionizes because of polymeric chains repulsions begins and lead to drug release profile of procaine-HCl [72].

The pH-sensitive polyacryrlic acid chains show that swelling provides control release kinetics mechanism of the temozolidine [73]. Glycol chitosan nanoparticles and grafting of dimethyl aminopropyl groups formulated nanogel notably increases the release of doxorubicin [74].

Displacement by Ions in the Environment: Nanogels that release drugs on the specific site of action due to the signal of environmental responses. POEOMA-like water-soluble polymers containing nanogels are biodegraded in glutathione tripeptide, which is generally found in cells. Cationic nanogels, when triggered with the negatively charged drug in cell membrane from complexes, explain the cellular accumulation of drugs delivered with nanogel [75].

Current Standing in Clinical Trials and Future Perspective of Nanogels: Nanogels are already in the application as drug delivery systems *in-vivo* and clinical trials, mainly for cancer care therapeutics. In mice with hypodermic fibrosarcoma, hypodermic injections of recombinant murine lymphokine-twelve (IL-12) encapsulated in nanogels, *via* incubation at temperature, semiconductor diode to a chronic elevation of IL-twelve within the sera and resulted in vital growth retardation.

TABLE 1: LIST OF MEDICINES FORMULATED IN NANOGEL

Drug Substance	Polymer or crosslinking agent used	Goal of Formulation	Method name	Ref.
Aegle marmelos (L.)		Preparation of solid lipid nanoparticles (SLNs) of Aegle oil (AO) that increases the antimicrobial potency		76
Pravastatin -Sod	Chitosan	Formulation of Pravastatin-loaded nanogel for examination its potency against hyperlipidemia	Ionic gelation method	77
Garlic Extract	Eudragit L100,	Development of Nanogel nanoparticles of garlic extract	Homogenization	78
Vitamin C	Bovine serum albumin Chitosan	Development of a formulation to increase the stability and absorption of the vitamin- C by preparing nanogels	Green self-assembly technique.	79
Artemether	Poloxamer 407, *Prosopis africana* peel powder	Formulation of transdermal nanogels using Nanostructured lipid carrier (NLC) ART-NLC	Homogenization	80
Ciclopirox-olamine	Eudragit-S100	Formulation of antifungal nanogel to reduce particle size, improve *in-vitro* and *in-vivo* release.	Homogenization technique	81
Montelukast Sodium		Preparation of Montelukast sodium niosomes and incorporation into the nanogel	Dispersion Method	82
Flurbiprofen	Pluronic F-127	Formulation of a thermosensitive *in-situ* nano gelling system to improve solubility and ocular residence time of flurbiprofen.		83
Clotrimazole	Locust bean gum and triethanolamine	Formulation, characterization and evaluation of the Clotrimazole nanogel.	Solvent diffusion method (high speed Homogenization)	84
Ketoprofen	Chitosan	Development and evaluation of nanoemulsion-based nanogel for transdermal delivery of ketoprofen.	Homogenization	85
Curcumin	Triethnolamine	Formulation and evaluation of the nanoemulgel for squamous cell carcinoma, enhancement of solubility, permeability and biocompatibility, also overcome the problem (targeted delivery) related with curcumin anticancer drug.	Spontaneous emulsifica-tion mechanism.	86
Beta Sitosterol	Eudragit RL100 and Poloxamer	Development of nanogel to reduce particle size for improvement of bioavailability a hydrophobic drug.	Nanoprecipitation method	87
Boswellia Serrata		Formulation of topical analgesic and anti-inflammatory nanoemmigel, a combination of a nanoemulsion and a nanomicellar system in a gel base.	Microemulsion-template method	88
Tenoxicam	Noveon Polycarbophil AA-1	Development of a tenoxicam nanogel to reduce particle size for improvement of the bioavailability	Modified emulsification-diffusion Method	89
Clindamycin Phosphate and *aloe vera*	Acrypol 940, Tefose 63	Formulation and evaluation of semi-herbal gel comprises of Clindamycin phosphate with *aloe vera*.	Homogenization	90
Aceclofenac		Formulation of nanosized dispersion of aceclofenac drug	Emulsion-solvent diffusion method	91
Flurbiprofen	Chitosan	Development and evaluation of nanoemulsion-based nanogel of Flurbiprofen for transdermal delivery		92
Curcumin	Amphiphilic Poloxamer-cationic network	Development and evaluation a novel colloidal nanogel carrier for encapsulation of curcumin to increase its solubility and cytotoxicity.	Homogeneous mixing	93

Future Prospective: Based on different studies discussed above in this current review, it can be interpreted that in the developing procedure of different novel drug delivery systems, nanogel has appeared as the best alternative for topical drug delivery. Nanogel has been developed to improve the poor bioavailability of uncountable drugs and enhance pharmacodynamics and pharmacokinetics. Presently, innumerable lipophilic drugs of a variety of therapeutic categories are being formulated as nanogel, possessing better therapeutic profiles. In the health care system, the nanogel is employed for lots of acute and chronic diseases *e.g.* inflammation, fungal diseases, psoriasis, cardiovascular problems, alopecia *etc*. With all these advantages of drug delivery, the future prospects of nanogel seem to be beneficial, and it may be predictable that nanogel as a delivery system will be optimism for diverse categories of medicines that have been removed from the pipeline of development due to various reasons *e.g.,* poor bioavailability, clinical potential *etc*.

Consequently, the major focus should be on enhancing and improving target potency for more effective skin care. Thus the researchers should aim generation or identification of novel nanomaterials that is biocompatible and biodegradable and has the potential to correct all the phases of the skin care process.

CONCLUSION: Facts established based on observation and experiments suggest that nanogel formulations can be a good alternate option for conventional drug delivery systems for BCS class II or IV drugs belonging to various pharmacological categories. It has also been observed that methods of preparation and participation of different components are key factors of dosage form stability and therapeutic activity. Though nanogel system comprises numerous components with diverse categories of surface-active agents, an improved concentration of which can precipitate mild to severe toxicological conditions, selection of components, and quantitative estimation of same should be considered as an issue of worry. Generally, with the references of all the above experimental studies and their results, it can be concluded that a nano-formulation-based gel system can be a secure and efficient drug delivery approach for recently approved active pharmaceutical ingredients. Nanogel is one of the attractive fields of analysis in the future, which can help deliver the drug in a controlled pattern while lowering the aspect result of typical nanogel. It has versatile advantages and properties that make them competent for the economical delivery of biologically active molecules, significantly biopharmaceuticals. They will even be used as a carrier or chaperoned to treat inheritable diseases such as cancer, neurodegenerative sickness, etc. Nanogel seems to be a wonderful formulation not only for skin care but also for treating varied diseasesincluding polygenic diseases.

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