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## FORMULATION AND EVALUATION OF MOISTURISING COLD CREAM WITH NATURAL ROSE EXTRACTS

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### ABSTRACT

A cream is a topical preparation usually for application to the skin. Creams for application to mucous membranes such as those of the rectum or vagina are also used. Creams may be considered pharmaceutical products as even cosmetic creams are based on techniques developed by pharmacy and unmedicated creams are highly used in a variety of skin situation (dermatoses). The use of the inger tip unit concept may be helpful in guiding how much topical cream is necessary to cover different areas. Creams are semi-solid emulsions, that is mixtures of oil and water. They are divided into two types: oil-in-water (O/W) creams which are composed of small droplets of oil dispersed in a continuous phase, and water-in- oil (W/O) creams which are composed of small droplets of water dispersed in a continuous oily phase. Oil-in-water creams are more comfortable and cosmetically suitable as they are less greasy and more easily washed off using water. Water-in-oil creams are more difficult to handle but many drugs which are integrated into creams are hydrophobic and will be released more readily from a waterin-oil cream than an oil-in-water cream. Water-in-oil creams are also more moisturising as they provide an oily barrier which reduces water loss from the stratum corneum, the outermost layer of the skin. Creams can be used for administering drugs via the vaginal route. Creams are used to help sun burns Composition: There are four main ingredients of the cream

- 1: Water
- 2: Oil
- 3: Emulsifier
- 4: Thickening agent

### INTRODUCTION

The skin is the largest organ of the human body and it is the first line of defense against the environment. It is composed of several layers, the outermost being the stratum corneum. The skin is constantly exposed to various environmental factors such as UV radiation, pollution, and dryness, which can lead to skin damage and aging. Moisturizing creams are used to help maintain the skin's natural barrier and prevent moisture loss. Natural rose extracts are known for their antioxidant and anti-inflammatory properties, making them a valuable ingredient in skin care products. This study aims to formulate and evaluate a moisturizing cold cream containing natural rose extracts.

**Types of Topical Dosage Forms:-**

Main topical dosage forms are

1. Ointment
2. Cream
3. Gel
4. Lotion

**CREAMS:**

**Definition:-** these are the semisolid preparation in which one or more medicament are dissolved either the w/o and o/w emulsion. A cream is a topical preparation usually for application to the skin. Cream for application to mucus membrane such as those of the rectum or vagina are also used. Creams may be considered pharmaceutical products as even cosmetics cream are based on techniques developed by pharmacy and unmedicated cream are highly used in a variety of skin condition. Creams are preferred to ointment because they are easier to spread and in case of o/w emulsion they are easier to remove.

Today, the use of cream cosmetics products has increased tremendously. Human contact to cosmetics formulations and their ingredients occurs primarily via the topical route such as cream and lotion. Several considerations are necessary regarding the appropriateness and safety of cosmetics, because cosmetics preparations are used nearly continually and in direct contact with the skin. Water in oil creams are also more moisturising as they provide an oily barrier which reduces water loss from the stratum corneum the outmost layer of the skin

**Types of cream:-**

Types of cream are:

- 1) Water in oil cream
- 2) Oil in water cream
- 3) Emulsion cream
- 4) Gel cream
- 5) Solid cream

**Advantages:-**

- 1) creams are less greasy and easy to applied.
- 2) cream produce cool effect due to evaporation of water and causes soothing effect on inflamed cream.
- 3) creams are less interfere with skin function and have more contact with skin than ointment.
- 4) creams are physically more stable.
- 5) they more stable as compare to liquid dosage form.

**Disadvantage:-**

- 1) they are bulkier than solid dosage form.
- 2) when applications of an exact quantity of ointment to the affected area is required ,it is difficult to as certain the same.
- 3) they are less stable than solid dosage . Different types of creams:
  - A. Cleansing cream
  - B. Massage creams
  - C. Night creams
  - D. Moisturizing creams
  - E. Foundation creams
  - F. Vanishing creams
  - G. All purpose cream.

## MOISTURISING COLD CREAM WITH NATURAL ROSE EXTRACTS:-

It is found to be one of the most popular and old preparation since long back, Galen is considered to be the founder of this cream. It must primarily possess an emollient action and is useful for dry skin and quite popular in winter. They provide a cooling effect on application, and this is due to the evaporation of water separated by breaking of w/o emulsion.

These contain a high percentage of mineral oil. These are o/w type. This cream contains a high amount of mineral oil for cleansing action.

Basically these are o/w type emulsion. After the cream is being rubbed into the skin, a satisfactory quantity of water evaporates to impart a phase inversion to the w/o type. The solvent action of the oil as the external phase imparts cleansing property.

In this type of cream, borax reacts with free fatty acids present in the bees wax and produces soft soap which acts as the emulsifying agent and emulsifies the oil phase. In cold creams, the internal phase is aqueous and the external phase is oil.

### Typical formulation:-

Bees wax ..... 2 gm  
 Borax ..... 2 gm  
 Almond oil ..... 50 gm  
 Rose water ..... 35.5 gm  
 Lanolin ..... 0.5 gm  
 Preservative and perfume ..... q.s.

### BEESWAX:-

**Ability to Protect from Irritants**—Beeswax can also act as a layer of protection when applied to the skin. It can protect skin from environmental irritants and extreme weather. **Promotion of Hair Growth**—Beeswax not only moisturizes and soothes hair, but it can keep moisture from getting out of the hair. Beeswax can create a protective layer on the skin. It's also a humectant, which means that it attracts water. Both of these qualities can help the skin stay hydrated. Beeswax is also a natural exfoliator, ideal for sloughing away dead skin cells. Beeswax heals and softens skin, and is an antibacterial agent. It can help you fight conditions like acne, dry skin, eczema, and stretch marks. Our raw beeswax can help you create your own skin care moisturizers and lotions specially formulated just for you.



### BORAX:-

Borax, combined with wax, is used in many cosmetic products like creams, gels, and lotions. It is famously used in hand soaps to help wash off the oil or grease from the hands. Borax's alkaline nature makes it a perfect ingredient in cleansers and toners. In cosmetic products, borax is sometimes used as an emulsifier, buffering agent, or preservative for moisturizing products, creams, shampoos, gels, lotions, bath bombs, scrubs, and bath salts. Borax is also an ingredient combined with glue and water to make "slime," a gooey material that many kids enjoy playing with. Right from creams and body lotions to shampoos, bath gels and even the in-vogue bath bombs, just about every product associated with skincare has Borax as one of its components. Given its mild and antiseptic nature, quite a few natural cosmetic products tend to include Borax as an essential ingredient as well.



### **ALMOND OIL :-**

*More than soothing dry skin, almond oil can improve complexion and skin tone. It's highly emollient, which means it helps to balance the absorption of moisture and water loss.*

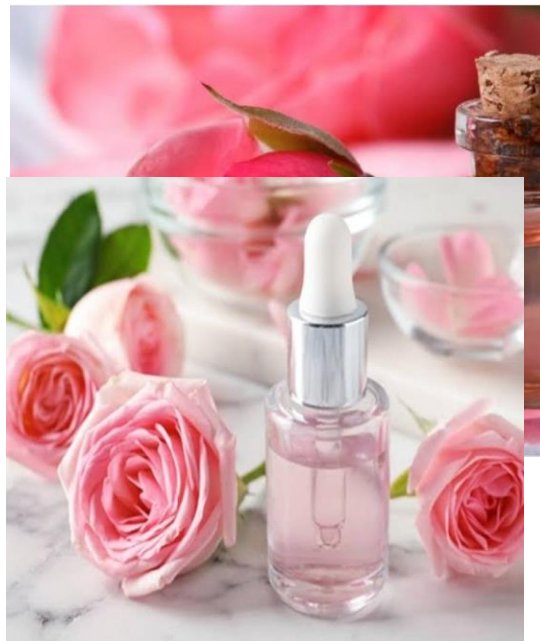
*Because it is antibacterial and full of vitamin A, almond oil can be used to treat acne. You can also use almond oil as a moisturizing oil. To do so, wash and dry your skin as usual. Then, gently pat a small amount of almond oil – about half the size of a dime – onto your face with your fingertips, and let it absorb into your skin. If you're using it as a moisturizer, you don't need to rinse it off. Almond oil is both a moisturizer and an emollient . Moisturizers supply water to the skin and hold it in with an oily substance. Emollients smooth the skin, filling in little gaps. Rather than adding moisture, they help the skin retain it by improving its barrier function.*



### **ROSE WATER:-**

*Rose water is especially hydrating when combined with other moisturizing ingredients, such as ceramides or glycerin. "These help to moisturize the skin, protect the skin barrier and prevent further water loss from the skin," says Allawh. However, it shouldn't replace your current moisturizer. Rose water has been used as a beauty product for thousands of years, so it's no surprise that it can improve your complexion and reduce skin redness. The antibacterial properties may help reduce acne. The anti-inflammatory properties can reduce skin redness and puffiness. Rose Water Maintains the Skin's Natural pH Balance. Chemically produced soaps and cleansers disrupt the pH balance of our skin, making it prone to bacteria that cause various skin conditions like rashes and acne..... This property helps rose water restore the skin to its normal pH level.*





#### LANOLIN:-

Lanolin is used as a moisturizer to treat or prevent dry, rough, scaly, itchy skin and minor skin irritations (e.g., diaper rash, skin burns from radiation therapy). Emollients are substances that soften and moisturize the skin and decrease itching and flaking.

#### RESERVATIVE:-



Vitamin E instead prevents oxidation of oils, which is why its called an antioxidant! Keep in mind Vitamin E is NOT an actual preservative and cannot be used as one in products containing water.



#### PERFUME:-

Step 1 – Pour about 1/3 cup of the unscented lotion into your small mixing bowl. Step 2 – Add about five to eight sprays of perfume into the lotion base. Add more if you want a stronger scented lotion ..... Step 4 – Using the funnel, pour the scented lotion mix into your lotion bottle. Perfume can last on your skin more than 24 hours. Most popular perfumes, however, tend to last anywhere between three and 12 hours. The perfumes and fragrances used in products can be tough on some skin tones and can actually cause negative reactions – especially if you have dry or sensitive skin. Also, If you have rosacea, psoriasis, or eczema, a fragrance-free moisturizer is much gentler on your skin.



#### Formulation of moisturising cold cream:-

Bees wax..... 2 gm  
 Borax .....2 gm  
 Almond oil .....50 gm  
 Rose water ..... 35.5 gm  
 Lanolin ..... 0.5gm  
 Preservative and perfume ..... q.s.

**Method of preparation:-**

- 1) dissolve the borax in hot water.
- 2) heat all the waxy materials and oil phases and heat those other material at 70c.
- 3) pour into the borax solution which is also maintained at the same 70c temperature.
- 4) then they are mixed to a homogenous mixture.
- 5) perfume can be added after bringing the temperature of the homogenous mixture to 45-50c.

**uses:-**

- . 1) heavily moisturises dry skin.
- 2) can also be used as a balm for dry cracked Lip's.
- 3) it can also be used as a shaving cream alternative for me
- 4)

**CREAM ABSORPTION THROUGH SKIN :-**

Two principal absorption routes are identified:

a) Transepidermal Absorption . b) Transfollicular Absorption

**a) Transepidermal Absorption:-**

It is now generally believed that the transepidermal pathway is principally responsible for diffusion across the skin. The resistance encountered along this pathway arises in the stratum corneum. Permeation by the transepidermal route first involves partitioning into the stratum corneum. Diffusion then takes place across this tissue. The current popular belief is that most substances diffuse across the stratum corneum via the intercellular lipoidal route. This is a tortuous pathway of limited fractional volume and even more limited productive fractional area in the plane of diffusion. However, there appears to be another microscopic path through the stratum corneum for extremely polar compounds and ions. Otherwise, these would not permeate at rates that are measurable considering their o/w distributing tendencies. When a permeating drug exits at the stratum corneum, it enters the wet cell mass of the epidermis and since the epidermis has no direct blood supply, the drug is forced to diffuse across it to reach the vasculature immediately beneath. The viable epidermis is considered as a single field of diffusion in models. The epidermal cell membranes are tightly joined and there is little to no intercellular space for ions and polar nonelectrolyte molecules to diffusively squeeze through. Thus, permeation requires frequent crossings of cell membranes, each crossing being a thermodynamically prohibitive event for such water-soluble species. Extremely lipophilic molecules on the other hand, are thermodynamically embarrassed from dissolving in the watery regime of the cell (cytoplasm).

Thus the viable tissue is rate determining when nonpolar compounds are involved. Passage through the dermal region represents a final hurdle to systemic entry. This is so regardless of whether permeation is transepidermal or by a shunt route. Permeation through the dermis is through the interlocking channels of the ground substance. Diffusion through the dermis is facile and without molecular selectivity since gaps between the collagen fibers are far too wide to filter large molecules. Since the viable epidermis and dermis lack measure physiochemical difference, they are generally considered as a single field of diffusion, except when penetrants of extreme polarity are involved, as the epidermis offers measurable resistance to such species.

**b) Transfollicular (Shunt Pathway) Absorption:-**

The skin's appendages offer only secondary avenues for permeation. Sebaceous and eccrine glands are the only appendages, which are seriously considered as shunts bypassing the stratum corneum since these are distributed over the entire body. Though eccrine glands are numerous, their orifices are tiny and add up to a minuscule fraction of the body's surface. Moreover, they are either evacuated or so copiously active that molecule cannot diffuse inwardly against the glands output. For these reasons, they are not considered as a serious route for percutaneous absorption. However, the follicular route remains an important avenue for percutaneous absorption since the opening of the follicular pore, where the hair shaft exits the skin, is relatively large and sebum aids in diffusion of penetrants. Partitioning into sebum, envisioned mechanism of permeation by point of systemic entry. Absorption across a membrane, the current or flux is and term of matter or molecules rather than electrons, and the driving force is a concentration gradient (technically, a chemical potential gradient) rather than a voltage drop. Membranes act as a "diffusional resistor." Resistance is proportional to thickness (h), inversely proportional to the diffusive mobility of matter within the membrane or to the diffusion coefficient (D), inversely proportional to the limited area of a route where there is more than one (F), and inversely proportional to the carrying capacity of a phase.



**EVALUATION TEST OF CREAM :-**

As per the requirements for skin creams specified, following parameters are used for evaluation of cream.

**a) Thermal stability :-**

For thermal stability testing, a humidity chamber and clear glass container of around 30ml capacities with screw cap are used. With the help of spatula cream is inserted in the glass containers and tapped to settle to the bottom and plug is inserted and tightens the cap.

The packed bottle is kept inside the incubator at  $450 \pm 10^\circ\text{C}$  for 48h. On removal from the incubator, it is noted that no oil separation or any other phase separation will not be observed, than formulated cream is stable at  $450^\circ\text{C}$ . The digital pH meter is calibrated using buffer solution of pH 4.01, 7.0 and 9.2. Cream is taken in a beaker and the pH of the cream is determined [30,31,31].

**b) Irritancy test:**

Mark an area (1sq.cm) on the left hand dorsal surface. The cream is applied to the specified area and time is noted. Irritancy, erythema, edema, is checked if any for regular intervals up to 24 hrs and reported [33,37,39].  
**Determination of total fatty substance content:-** About 2g of the exactly weighed formulated cream is taken into a conical flask, Dilute Hydrochloric acid (25ml) is added and a reflux condenser is fixed into the flask and the solution is boiled until it completely cleared. Then contents of the flask are poured into a 300ml-separating funnel and it is cooled to room temperature. In portion of 10ml the conical flask is rinsed with 50 ml of petroleum ether and poured into the separating funnel, separating funnel is then shaken well and left until the layers are separated. An aqueous phase is separated and all ether extract is then washed with water. This petroleum ether extract is then filtered through a filter paper and dried the material in the flask at a temperature  $90 \pm 20^\circ\text{C}$  to constant mass [39].

**Formula:-**

Total fatty substance =  $100 M1 / M2$  Where,

$M1$  = mass (g) of the residue  $M2$  = mass (g) of the cream **Determination of residue:-**

About 5g of the cream is taken in a weighed, clean and dry squat form weighing bottle and dried to constant mass at  $105 \pm 10^\circ\text{C}$ . Cooled in a desiccator and weighed [31,37,38].

**Formula:**

Residue =  $100 M1 / M2$  Where,

$M1$  = mass (gm) of the residue  $M2$  = mass (gm) of the cream **Test for lead:-**

Standard lead solution is prepared by using 1.600gm of the lead nitrate taken in water and the solution is made to 1000ml. solution (10ml) is pipette out and diluted to 1000ml with water. 1 ml of this solution contains 0.01mg of lead (Pb). About 2.00gm of cream is taken in a crucible and heated on a hot plate and then taken in a muffle furnace to ignite it at  $600^\circ\text{C}$  to constant mass. Dilute hydrochloric acid 3ml (5N) is added and warmed and volume is made to 100ml. solution is then filtered. In the second Nessler's cylinder, 2 ml of dilute acetic acid (1N) is added, volume is made with water to 25ml. standard hydrogen sulphide (10ml) solution is added to each Nessler's cylinder and volume is made with water (50ml) mixed and allowed to stand for 10min and the colour produced in two Nessler's cylinders is compared. The colored produced with hydrogen sulphide is matched against that obtained with standard lead solution [39,39].

**c) Spreadability:-**

Spreadability of cream is measured with the glass slide apparatus, overkill of cream is placed between two slides and 1 kg weight is placed on slide for 5 min. to compress the sample to uniform thickness, time in seconds to separate two slides is taken as measure of spreadability [31,34,39].  $S = w / l / t$  where,

$S$  = spreadability (g cm/sec)  $w$  = weight on upper slide (g)  $l$  = length of Slide (cm)

$t$  = time taken in sec (sec)

**C) Homogeneity:-**

The developed cream is tested for homogeneity by visual inspection, after the cream have been set in the container, spread on the glass slide for the appearance, tested for the presence of any lumps, flocculates or aggregates [33,37,39].

**d) Consistency:-**

Consistency of the formulation is determined by penetrometer [32,37,39].

**e) Microbial evaluation:-**

Microbial evaluation of herbal formulations is essential to check the limit microbial contamination and extents of pathogenicity. This evaluation has direct correlation with the quality of products. For the evaluation of total microbial count details of different count media are used, nutrient agar medium used for the growth of bacteria and Potato dextrose agar medium is used for the growth of fungi. In aseptic conditions cream equivalent to 1 gram is dissolved in 10ml of sterile water and is serially diluted. The medium and apparatus required for experimental are sterilized in an autoclave at  $121^\circ\text{C}$  for 15min. In aseptic



conditions, 1ml of test sample is transferred to petridish containing melted agar medium at about 42 0 C and mixed well by rotating the petridish. It is allowed to solidify and then incubated at 37 0 C for 24h for detection of bacteria. After incubation period, colonies are counted[33,31,39].

#### F) Rheology:-

The rheological parameters are vital for this cosmetics preparation as there disperse partials may tend to settle during the storing period. they exhibit non-newtonian flow. There for , corresponding viscometer should be used for determining there flow properties.

#### G) sensitivity test:-

certain products are allergic or super sensitive to skins the test sample is applied along with a marked sample Ata different areas over the in and are compared for any allergic reaction. Sensitization of skin is measured with patch test. Patch test is normally open or occlusive.

The test sample is applied along with a standard market product at different places of skin and effect is compared after a period of time.

#### H) biological testing:-

this is essentially for products having antiseptic,harmons,vitamins etc.that can be evaluated using suitable methods(microbiological,animal studies).

Appearance: -The appearance of the cream is judged by its color, pearlscence and roughness and graded[22,26,28].

After feel:

Emolliency, slipperiness and amount of residue left after the application of fixed amount of cream is check.

Type of smear:

After application of cream, the type of film or smear formed on the skin are check[24]. Removal: The ease of removal of the cream applied is examined by washing the applied part with tap water[24].

Acid value:

Take 10 gm of substance dissolved in accurately weighed, in 50 ml mixture of equal volume of alcohol and solvent ether, the flask is joined to reflux condenser and slowly heated, until sample is dissolved completely, to this 1 ml of phenolphthalein added and titrated with 0.1N NaOH, until faintly pink color appears after shaking for 30 seconds[26,35].

Acid value =  $n \times 5.61 / w$

n = the number of ml of NaOH required. w = the weigh of substance.

Saponification value:

Introduce about 2 gm of substance refluxed with 25 ml of 0.5 N alcoholic KOH for 30 minutes, to this 1 ml of phenolphthalein added and titrated instantly, with 0.5 NHCL[28,30,38]. Saponification value =  $(b - a) \times 28.05 / w$

The volume in ml of titrant = a The volume in ml of titrant = b

The weigh of substance in gm = w

l) viscosity:- to obtain a consistent quality, viscosity of cream and lotion should be measured during manufacturing process. viscosity of cream and lotion are non Newtonian in nature that should remain constant throughout there shelf life. A ford viscosity cup or a Brookfield viscometer can be used to measure viscosity of cream. If the viscosity is high, it can be corrected adding additional fatty material and emulifier.

#### APPLICATIONS OF CREAM:-

In order to formulate an effective and efficient cream preparation,deliberation must be given to the intended purpose. This is directly concerned with the site of action and the desired effect of the preparation. Cream preparations may be used for.

1) **Surface Effects:-** Cleansing (removal of dirt and germs), Cosmetics (enhancemen appearance),Protective (prevention of moisture loss, sunscreen), Antimicrobial (reduction of infection).

#### 2) Stratum Corneum Effects:-

Protective (e.g. sunscreens that penetrate this layer), keratolytic (a sloughing of the skin,useful in the treatment of psoriasis), protective (moisturising)

#### 3) Viable Epiermal and Dermal Effects:

Several classes of drugs may pierce to these layers (anti- inflammatory, anesthetic, and antipruritic, antihistamine). Although it is difficult for drugs to penetrate the stratum corneum, once they are in the dermis, they can diffuse into the general circulation. It is difficult to formulate a drug with only a local effect without subsequent uptake by the bloo.

**4) Systemic Effects:-**

A few drugs, such as Scopolamine, Nitroglycerin, Clonidine, and Estradiol, have been formulated in a manner to achieve systemic effects.

**5) Appendage Effects:-**

Some classes of drugs are intended to exert their action in these portions of the skin (depilatory, exfolient, antimicrobial, and antiperspirant).

**REFERENCE**

1. Gollnick H. Current concept of the pathogenesis of acne: implications for drug treatment drugs 2003; 63:1579-96.
2. Shalita A. The integral role of topical and oral retinoids in early treatment of acne. *J Eur Acad Dermatol Venereol* 2001; 15(Suppl 3):43-9.
3. Thiboutot D. New treatment and therapeutic strategies for acne. *Arch Fam Med* 2000; 9:179-87.
4. Cunliffe WJ, Gollnick HPM. Acne: diagnosis and management. London: Martin Dunitz, 2001.
5. Plewig G, Kligman AM. Acne and rosacea, 4th ed. Berlin: Springer-Verlag, 2002.
6. Russell J.J. Topical therapy for acne. *AM Fam Physician* 2000;61:357-66.
7. Dreno B, Poli F. Epidemiology of acne. *Dermatology* 2003;206:7-10.
8. Gollnick H, Schramm M. Topical treatment in acne. *Dermatology* 1998; 196:119-25.
9. Gollnick HP, Krauthaim A. Topical treatment in acne: current status and future aspects. *Dermatology* 2003; 206:29-36.
10. Ktauthaim A, Gollnick H. Transdermal penetration of topical drugs used in the treatment of acne. *Clin Pharmacokinet* 2003;42:1287-1304.
11. Stuttgen G. Historical perspective of Tretinoin. *J Am Acad Dermatol* 1986;15:735-40.
12. Zouboulis CC, Orfanos CE. Retinoids. In: Millikan LE, editor. Drug therapy in dermatology. New Orleans: Dekker, 2000:171-233
13. Gollnick H, Schramm M. Topical therapy in acne. *J Eur Acad Dermatol Venereol* 1998;11 (Suppl 1):S8-12.
14. Gollnick HP, Dummler U. Retinoids. *Clin Dermatol* 1997;15:799-810.
15. Orfanos CE, Zouboulis CC, Almond-Roesler B, et al. Current use and future potential role of retinoids in dermatology. *Drugs* 1997; 53:355-88.
16. Thielitz A, Helmdach M, Ropke EM, et al. Lipid analysis of follicular casts from cyanoacrylate strips as a new method for studying therapeutic effects of antiacne agents. *Br J Dermatol* 2001;145:19-27.
17. Gollnick H, Cunliffe W, Berson D, et al. for the Global Alliance to Improve Outcomes in Acne. Management of acne: a report from a Global Alliance to Improve Outcomes in Acne. *J Am Acad Dermatol* 2003; 49:S1-37.
18. Leid M, Kastner P, Chambon P. Multiplicity generates diversity in the retinoic acid signalling pathways. *Trends Biochem Sci* 1992;17:427-33.
19. Zouboulis CC. Retinoids— which dermatological indications will benefit in the near future? *Skin Pharmacol Appl Skin Physiol* 2001; 14:303-15.
20. Nagpal S, Chandraratan RA. Recent developments in receptor-selective retinoids. *Curr Pharm Des* 2000;6:919-31.
21. Griffiths CE, Voorhees JJ. Human in vivo pharmacology of topical retinoids. *Arch Dermatol Res* 1994; 287:53-60.
22. Chandraratana RA. Future trends: a new generation of retinoids. *J Am Acad Dermatol* 1998;39:S149-52.
23. Nagpal S, Cai J, Zheng T, et al. Retinoid antagonism of NF-IL6: insight into the mechanism of antiproliferative effects of retinoids in Kaposi's sarcoma. *Mol Cell Biol* 1997;17:4159-68.
24. Nagpal S, Athanikar J, Chandraratna RA. Separation of transactivation and API antagonism functions of retinoic acid receptor alpha. *J Biol Chem* 1995;270:923-7.
25. Zouboulis CC, Orfanos CE. Retinoids. In: Millikan LE, editor. Drug therapy in dermatology. New Orleans: Dekker, 2000:1171-233.
26. Wolf JE, Jr. Potential anti-inflammatory effects of topical retinoids and retinoid analogues. *Adv Ther* 2002;19:109-18
27. Sardana K, Sehgal VN. Retinoids: fascinating up-and-coming scenario. *J Dermatol* 2003;30:355-80.
28. Lammer EJ, Chen DT, Hoar RM, et al. Retinoic acid embryopathy. *N Engl J Med* 1985; 313:837-41
29. Lipson AH, Collins F, Webster WS. Multiple congenital defects associated with maternal use of topical Tretinoin. *Lancet* 1993;341:1352-3.
30. Camera G, Pregliasco P. Ear malformation in baby born to mother using Tretinoin cream. *Lancet* 1992;339:687.
31. Camera G, Pregliasco P. Ear malformation in baby born to mother using Tretinoin cream. *Lancet* 1992;339:687.
32. Rosa F. retinoid embryopathy in humans. In: Karen G, editor. Retinoids in clinical practice. New York: Dekker, 1992:77-109.
33. Jick SS, Terris BZ, Jick H. first trimester topical Tretinoin and congenital disorders. *Lancet* 1993;341:1181-2.

34. Lucky AW, Cullen SI, Funicella T, et al. double-blind, vehicle-controlled, multicenter comparison of two 0.025% Tretinoin cream in patients with acne vulgaris. *J Am Acad Dermatol* 1998; 38:524-30.

35. Kathleen Parfitt. *Martindale The complete drug references*. 32nd ed. London: Pharmaceutical press 1999; 61-62.

