CHAPTER – 02

LITERATURE REVIEW

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2.1. Skin Infection and Role of Topical Antimicrobial Agents an overview

The skin presents a first line of defence against a wide range of bacterial pathogens. When the integrity of the skin is compromised accidentally or intentionally, its natural defences weaken and a role for antibacterial emerges. The topical route of application offers several advantages over systemic administration, including the avoidance of systemic toxicity and side effects, the decreased induction of bacterial resistance, and a high concentration of antibacterial agent at the site of infection. A treatment that must be physically applied to the skin is limited, however, by patient compliance, local side effects such as allergic contact dermatitis, and the depth of penetration of the agent. Despite their shortcomings, topical antibacterial agents are highly versatile and can be used successfully for both prophylaxis and treatment of bacterial infections. Outside of the hospital setting, *Staphylococcus aureus* and *group A streptococci* are classically considered as the pathogens most often involved in infections of the skin. Recent data from hospitalized patients demonstrate that *S aureus*, *Enterococcus spp*, coagulase-negative *staphylococci*, *Escherichia coli*, and *Pseudomonas aeruginosa* are the most prevalent pathogens involved in skin and soft tissue infections [Jones et.al--2003] 22.

**Resident skin flora**

The skin normally provides host to a number of bacteria, fungi, and even mites (i.e., *Demodex spp*). Coagulase-negative *staphylococci* represents the dominant bacterial resident within the stratum corneum and on the skin surface with a reservoir in the sebaceous glands.

**Superficial wounds**
A landmark study on the natural history of superficial wound infection demonstrated a 47% streptococcal colonization rate of minor skin trauma (largely mosquito bites and abrasions) in a control group [Maddox et.al.-1985] 23. The same study showed that antibiotic ointment containing bacitracin, polysporin, and neomycin decreased this rate to 15% when applied thrice daily. Topical antibacterial agents also seem to have effects on wound healing in a manner seemingly unrelated to their antimicrobial properties. Ointment containing bacitracin, polymyxin, and neomycin has been shown to increase the re-epithelialization rate of experimentally induced wounds by up to 25% [Geronemus et.al.-1979] 24 and minimize scarring and dyspigmentation compared with other agents and placebo [Berger et.al.-2000] 25.

**Operative wounds**

**Postoperative wound care**

Despite their excellent preoperative performance, disinfectants such as chlorhexidine and povidone-iodine are generally not helpful in preventing infections when applied to postoperative wounds. Moreover, many experimental studies have demonstrated significant cytotoxicity from these agents [De Jong et.al.--1982, Tatnall et.al.--1990, Tatnall et.al.--1991, Brown et.al.-1993] 26-29. Better suited for this task are topical antibacterial agents such as bacitracin, mupirocin, and silver sulfadiazine which seem to decrease infection rates and enhance wound healing [Leyden et.al.-1978, Watcher et.al.-1989, Forbes et.al.-1961] 30-32. In one large study of 6000 surgical cases, neomycin-bacitracin-polymyxin spray was found to decrease infection rates [Fielding et.al.-1965] 33. In a mouse surgical wound model, mupirocin cream showed equal efficacy to the oral penicillin flucloxacillin and greater efficacy than oral erythromycin in reducing bacterial counts. It was also
similar in efficacy to oral cephalexin against *Streptococcus pyogenes* but superior against *S. aureus* [Gisby *et al.*-2000] 34. Honey has been studied in a number of clinical settings, including as an agent for wound healing. The hyperosmolarity of honey impedes bacterial growth, whereas factors in honey called inhibines, which include flavonoids, and phenolic acids, seem to elicit antibacterial effects directly [Wahdan *et al.*-1998] 35. A systematic review of the data on honey concluded that, with some reservation because of the study quality and small numbers, wound healing and infection rates were consistently better in those patients treated with topical honey compared with several other active agents [Moore *et al.*-2001] 36.

**Burns**

The moist necrotic tissue in a burn patient is an ideal environment for bacterial growth. The large areas of ischemic tissue around the wounds may limit the availability and the usefulness of systemic antibiotics. Before 1965, the rate of burn wound sepsis was reported to be as high as 60%; this quickly fell to 28% after the widespread use of topical silver nitrate [Fraser *et al.*-2004] 37.

**Impetigo**

Impetigo is a superficial skin infection, which can be divided into primary skin infections (arising in previously intact skin) and secondary skin infections (arising in skin that has had barrier damage, such as secondary to dermatitis). Whether the infection is primary or secondary, the skin manifestation is classically a superficial erosion and honey-colored crust. *S. aureus* and *S. pyogenes* are most often the causative agents. A Cochrane systematic review of impetigo [Koning *et al.*-2004]38 and a large, recent systematic review [George *et al.*-2003]39 highlighted the following points:
• The peak incidence occurs between the ages of 2 and 6 years.
• Topical antibiotics are more effective than placebo.
• There is evidence that topical antibiotics are more effective than some systemic antibiotics for the treatment of impetigo.

Topical antibiotics are the preferable first-line treatment. Mertz et al. 1989 compared oral erythromycin with topical mupirocin in 75 patients with impetigo and the report showed that topical mupirocin performed superiorly than oral erythromycin. Another more recent study in 159 patients with secondarily impetigonized eczema demonstrated that mupirocin cream applied thrice daily was superior bacteriologically to oral cephalixin [Rist et al. 2002] 41.

2.2. Need for new antimicrobials

Topical antimicrobial agents, both antiseptics and antibiotics, are currently used to reduce the risk of infection. Although microbial resistance rates are not equally distributed around the world, microbial resistance to antibiotics has become a worldwide medical, economical, and public health problem. The overuse, misuse, and widespread prophylactic use of antimicrobial drugs are some factors leading to the emergence of drug resistant microorganisms [Milatovic et al. 1987] 10. Unlike antibiotics, antiseptics are potentially toxic, not only to microbial cells but also to host cells [Brennan et al. 1985] 11. Therefore, topical antiseptics should be used only where they are clinically indicated and only for limited periods that too under the specialist guidance. As the development of bacterial resistance to antibiotics and the controversy regarding the use of topical antiseptics persist, man turned to his prehistory and found literally thousands of phytochemicals from plants which inhibit
all types of microorganisms. These were safe and broadly effective agents which do not induce microbial resistance.

2.3. Herbals as a source of antimicrobials

The antimicrobial compounds from plants may inhibit bacterial growth by different mechanisms than those presently used antimicrobials and may have a significant clinical value in the treatment of resistant microbial strains [Eloff et al.-1988] 12. According to Olukoya et al.-199342 Herbal treatments is one possible way to treat diseases caused by multi drug resistant bacteria. According to the WHO, medicinal plants would be the best source for obtaining a variety of drugs. About 80% of the population of the developed countries use traditional medicines, derived from medicinal plants. Therefore, there is a vital need for thoroughly investigating such plants, determining the structural and functional properties of their constituents and develop them into magic bullet to treat various disease conditions.

2.4. Gels as topical drug delivery systems

Different strategies have been proposed to achieve efficient drug delivery systems and in the last few years hydrogels and gels in general have been considered as good candidates for oral, rectal, ocular, cutaneous and subcutaneous administration of drugs. Hydrogels in particular have been widely utilized in the medical and pharmaceutical field for their biocompatibility and their similarity to a natural tissue [Ratner et al.-1976, Peppas et al.-2000] 43,44.

Gels are semisolid systems in which the movement of the dispersion medium is restricted by interlacing three dimensional network of particles or solvated macromolecules of dispersed phase. The increased viscosity caused by interlacing
and consequential internal friction is responsible for the semisolid state. A gel may also consist of twisted and matted strands often tied together by stronger types of Vander Waals forces to form crystalline and amorphous regions throughout the system.

Concentration of gelling agents is usually between 0.5 to 2%, and gels maintain their viscosity over a wide range of temperatures. The use of gel as a delivery system can increase the residence time of drugs on the skin and, consequently, enhance bioavailability [Mathy et al.-2005] 45. Gel delivery systems have several advantages such as the ease of administration, none greasiness, patient compliance, high residence time on the skin and better drug release and diffusion [Kumar et al.-1995, Jones et al.-1999, Ramarao et al.-1996]46-48.

Chowdary et al- 199649 prepared eight semi solid formulations of ciprofloxacin belonging to anhydrous, cream (o/w and w/o) water soluble and gel categories and evaluated them for drug release, antibacterial and anti-fungal activities. Ciprofloxacin release from monophasic systems (anhydrous, PEG base and gels) followed zero order kinetics and biphasic system (creams) followed square root of time release order. Comparatively, PEG and gel formulations gave higher release rate and exhibited higher antibacterial and anti-fungal activities when compared to cream and anhydrous bases.
2.5. Polymer of Interest

Among polymers used for the formation of gel base, carbomer resin (carbopol) is used as gelling agent. A 1%w/w solution in water gives a pH of 3; viscosity of carbopol gel depends on the pH. An increase in pH in the range of 6-8 increases the viscosity and the adhesive properties of the gel.

Polymer Profile 43-46

In the present study, carbopol 940 was selected, since it exhibit required gel forming characters as compared with other polymers. The solubility of polymer was tested in various solvents and the best solvent in which the polymers are soluble was selected.

CARBOMER 43-52,112

Carbomer polymers are polymers of acrylic acid cross-linked with polyalkenyl ethers or divinyl glycol.

Synonyms: Carbopol

Carboxy poly methylene
Carboxy vinyl polymer
Carboxy acid polymer.

Chemical Name: Carboxy polymethylene.

Category: NF: Suspending agent and viscosity increasing agent.
BP: Pharmaceutical aid

Empirical Formula: (C_2H_4O_2) x (C_3H_5-Sucrose) y.

Molecular Weight: carbomer940- 9.4x10^6
Structural Formula:

![Structural Formula Image]

**Descriptions**

A white, fluffy, acidic, hygroscopic powder.

**Potential health hazards**

Eye: May cause irritation.

Skin: May cause irritation

Ingestion: No hazards expected in normal industrial use.

Inhalation: May cause respiratory tract irritation.

**Stability and storage conditions**

Dry powder forms of carbomer do not support the growth of moulds and fungi but microorganisms grow well in unpreserved aqueous dispersions. Dispersions maintain their viscosity on storage during prolonged periods at room temperature or at elevated temperature when stored away from light or with the addition of an antioxidant. Carbomer is a commonly used gelling agent that produces gels having a number of desirable characteristics. There are different grades available like 940, P934 (NF), 941, P974.

It is a synthetic high molecular weight polymer of acrylic acid cross linked with allyl sucrose and containing 56 to 68% of carboxy groups calculated as a dry substance. It is soluble in water, alcohol and glycerol which is neutralized by alkali hydroxides or amines. The polymer is hydrophilic and produces sparkling clear gels.
when neutralized. Gelation mechanism depends on neutralization of the carboxylic acid moiety to form soluble salt. Carbomer gel possesses good thermal stability in that gel viscosity and yield value are essentially unaffected by temperature. Carbomer gel posses optimum rheological properties. The inherent pseudo plastic flow permits immediate recovery of viscosity when shear is terminated and the high yield value and quick break make it ideal for dispensing gel formulations. Before neutralization, carbomer in water exists in unionized form yielding a thin opalescent dispersion of approximately pH3. At this pH the polymer is very flexible and behaves like a random cell. Addition of alkali hydroxide or neutralizing amine to the dispersion shifts the ionic equilibrium in favour of the –COOH groups and the polymer becomes stiff and rigid, thereby increasing the viscosity of the water. The peculiar structure of neutralized carbapol gel could be the prime cause for the semi rigid gel consistency of the carbapol gels and for the controlled drug release when drug molecules are incorporated into the gel matrix. Over neutralization and excess salts increase the viscosity of carbomer gels or cause precipitation by the counter ion effects

2.6. Selection of Permeation Enhancers

The permeation enhancers were selected based upon their solubility and miscibility with the solvent used and their efficiency as enhancers. The irritant property of the enhancer was also taken into consideration. Thus the three enhancers selected were Dimethyl formamide, Dimethyl Sulphoxide (DMSO) and Polyethylene glycol-400(PEG-400).
DIMETHYL FORMAMIDE (DMF) 51,52,112

Chemical Name:

N,N-dimethylformamide

Structural Formula:

HCON(CH$_3$)$_2$

Description:

DMF, is a clear, colorless, hygroscopic liquid with a slight amine odour. The solvent properties of DMF are particularly attractive because of the high dielectric constant, the aprotic nature of the solvent and low volatility. It is frequently used for chemical reactions and other applications which require a high solvency power. DMF is well established as a universal solvent.

Stability.

Dimethylformamide is hygroscopic and it is advisable to store it under nitrogen.

Effects in Humans

In humans, DMF is absorbed by inhalation and through the skin. High exposures to it (up to 60Ppm or 80µg/ml) causes headaches, abdominal pain, nausea, vomiting, dizziness and elevated liver enzymes. Alcohol intolerance is also seen.

Applications

Dimethylformamide is primarily used as an industrial solvent. Dimethylformamide solutions are used to process polymer fibers, films, and surface coatings and to permit easy spinning of acrylic fibers; to produce wire enamels, and as a crystallization medium in the pharmaceutical industry.
DIMETHYL SULFOXIDE (DMSO) 51,52,112

Definition:

DMSO is the organosulfur compound with the formula \((\text{CH}_3)_2\text{SO}\).

Synonyms: Methyl sulfoxide, sulfinylbis [methane]

Description:

Appearance: colorless liquid
Odor: odorless
pH: 8.5 (50/50 in water)
Boiling Point: 189oC (372oF)
Flammable limits (% in air): 3.0 - 3.5% by volume
Specific Gravity: 1.1 at 20oC (68oF) (water = 1)
Solubility in water at 20oC: Miscible
Octanol/Water Partition Coefficient: logPow = -2.03
Viscosity at 25oC (77oF): 2.0 mPa.s or cP
Melting Point: 18oC (64oF)
Stability: Stable

Acute Toxicity Data:

Oral LD-50 (male rat): 14,500-28,300 mg/kg
Inhalation (rat): No mortality rate @ 2,900 mg/m3 (900 ppm)/ 24 hrs.
Dermal LD-50 (rat): 40,000 mg/kg

Applications

It is an important aprotic solvent which is less toxic. It is also extensively used as an extractant in biochemistry and cell biology. DMSO plays a role in sample management and high-throughput screening operations in drug design.
POLYETHYLENE GLYCOL-40051,52,112

Definition:

Polyethylene glycol is a condensation polymer of ethylene oxide and water with the general formula \( \text{H(OCH}_2\text{CH}_2\text{)}_n\text{OH} \), where \( n \) is the average number of repeating oxyethylene groups typically from 4 to about 180.

Chemical Formula

\[ \text{H(OCH}_2\text{CH}_2\text{)}_n\text{OH} \]

Description

PEG - 400 is harmless to the skin. It is easily soluble in water and faintly sweet in taste. It imparts smoothness to skin but does not have a strong dehydrating effect as glycerine. PEG - 400 is a superior and thermally stable heating medium than the conventional mediums due to its higher molecular weight, higher boiling point and specific heat.

Applications:

It is used as a base for formulations like cream, emulsions.

**Adriana *et.al.*-2009 53** studied the antibacterial and antifungal activity as well as mutagenicity of *Sechium edule* fluid extract and to obtain a pharmaceutical formulation with them. The extract exhibited antimicrobial activity against *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Enterobacter cloacae, Serratia marcescens, Morganella morganii, Acinetobacter baumannii, Pseudomonas aeruginosa, Stenotrophomonas maltophilia, Candida spp. and Aspergillus spp.* Mutagenicity on both *Salmonella typhimurium TA98 and TA 100* strains until
100μg/plate were observed. A hydrogel with carbopol acrylic acid polymer containing *S. edule* fluid extract as antibacterial, antymycotic and antioxidant agent was obtained. Microbiological, physical and functional stabilities of pharmaceutical formulation stored at room temperature for 1 year were determined. The semisolid system showed antimicrobial activity against all Gram positive and Gram negative bacteria and fungi assayed. The minimal inhibitory concentration (MIC) values ranged from 20 to 800μg/ mL. Its activity was compared with a pharmaceutical formulation containing commercial antibiotic and antifungal agents. Pseudoplastic behavior and positive thixotropy were observed.

*Ibrahim et al -200954* studied wound healing properties of chitosan with different molecular weight. The macroscopic image and histopathology were examined using chitosan, Fucidin R ointment and to blank. The rate of contraction of wound surface was evaluated by determination of the unclosed area as a function of time. The treated wounds were found to contract at the highest rate with high molecular weight–high degree of deacetylation chitosan-treated rats as compared to untreated, treated, and Fucidin R ointment-treated rats. Wounds treated with high molecular weight chitosan had significantly more epithelial tissue (p < 0.05) than wounds with any other treatment. The best re-epithelization and fastest wounds closure were found with the high molecular weight chitosan treatment group. Histological examination and collagenase activity studies revealed advanced granulation tissue formation and epithelialization in wounds treated with high molecular weight chitosan (p < 0.05). High molecular weight with high degree of deacetylation chitosan samples, therefore, have good potential use as a treatment system for dermal burns.
**Shishu et al - 2006** made an attempt to prepare topical formulations of griseofulvin that can deliver the drug locally in effective concentration. Various hydrogel formulations were prepared using carbomer (940 NF) as base and essential oils, propylene glycol (PG), N-methyl-2-pyrrolidone (NMP) as penetration enhancers. The *in vitro* skin permeation studies through Laca mouse skin were performed using vertical type cells. PG in the hydrogel formulation was found to influence drug release rate by increasing its solubility and partitioning. Further, combinations of PG with varying amounts of NMP in the hydrogel formulations exhibited a significantly greater increase in the flux on comparison with the control and formulation containing PG alone. The prepared hydrogels did not show any skin sensitization and histological studies were carried out to check the safety of permeation enhancers used. Further these formulations were found to be stable at three different temperatures 4°, 25° and 40°C with respect to percent drug content, release characteristics, pH, transparency, feel and viscosity.

**Gregorios et al – 2004** studied the *in vitro* skin permeation of furosemide, a commonly used loop diuretic, through human epidermis, as a preliminary step towards the development of a transdermal therapeutic system. A screening study was carried out, in order to estimate the effects of the type, the concentration of enhancer and the concentration of gelling agent on the cumulative amount of furosemide permeated through human epidermis, using a 3x3 factorial design. The type and the concentration of enhancer were further evaluated as they were found to affect furosemide permeation significantly. In order to further increase the amount of the drug permeated, the combination of two enhancers, Azone® and oleyl alcohol, at three concentration levels was employed, using an optimization technique. The results indicated that higher amounts of furosemide permeated were observed when
Azone® was used at 5.0–6.5% (v/v) and oleyl alcohol at 7.5–9% (v/v), in the gels used. These formulations seem to be suitable for possible transdermal delivery of furosemide for pediatric use.

Jantharaprapap et al-2007\textsuperscript{57} was studied the effect of four different combinations of co-solvents (ethanol, glycol-PEG-400, propylene glycol, and water) on Meloxicam (MLX) \textit{in vitro} permeability through isopropyl myristate (IPM)-saturated cellulose membranes. The gel consisting of 2.5% Klucel, propylene glycol, ethanol, and water (1:1:1) showed superior permeability properties and it was selected as the base-gel to investigate the effect of three levels of the penetration enhancers: dimethylsulfoxide (1, 5, and 10% DMSO), tween20 (1, 2, and 5% TW20), oleic acid (0.4, 1, and 5% OA), and menthol (1, 2.5, and 5% MT). \textit{In vitro} permeability was determined throughout IPM-saturated cellulose membranes and human cadaver skin. DMSO and TW20 did not improve permeability of MLX compared to the control gel at any of the levels tested. Menthol produced a statistically significant (P < 0.001), dose proportionate increase in MLX flux with a peak at 5% (2.43±0.47μg/cm²/h). Conversely, addition of OA peaked at 1% but decreased at the higher level (5%). There was no significant difference between the MLX amount recovered in stratum corneum and dermis across the different formulations tested. These findings show that the 0.3% MLX gel formulation containing 5% menthol can possibly deliver therapeutically significant doses of MLX.

Das et al – 2007\textsuperscript{58} made an attempt to develop topical gel formulations of rofecoxib with Hydroxypropylmethylcellulose (HPMC), sodium alginate and Carbopol 940. The effects of polymer composition on the rate of drug release from
the gel formulations were examined through cellulose membrane mounted on a Keshary-Chien diffusion cell. The effects of initial drug concentration and viscosity on the permeation rate of rofecoxib from the gel formulations were evaluated using rat epidermis at 37 ± 0.5 degrees C. The anti-inflammatory activity of the rofecoxib gel formulation was evaluated using the rat hind paw edema model. The gel formulation consisting of 4% w/w sodium alginate-Carbopol 940 at 3:1 ratio was found to be suitable for topical application based on in vitro evaluation and ex vivo permeation studies. The drug permeation rate increased with an increase of the initial drug concentration in gels up to 25% w/w. An inverse relationship was observed between the in vitro drug release rate / ex vivo permeation rate and viscosity of the gel formulations. The anti-inflammatory activity of 4% w/w sodium alginate-Carbopol 940 gel containing 25% w/w rofecoxib in the rat hind paw edema model revealed that the drug was delivered to the inflammation site at a controlled level over a period of 6 h. These results suggest the feasibility of the production of topical gel formulation of rofecoxib.

Ozsoy et al -2004\textsuperscript{59} investigated the in vitro release properties of tiaprofenic acid (TA) from different topical vehicles. Carbopol® 940 gel, chitosan gel, two types of emulsion-based ointment formulations (o/w and w/o) and hydrophilic petrolatum USP were prepared with 2% drug content. Drug release from all vehicles through a standard cellophane membrane was evaluated by using Franz-type diffusion cells. In vitro release study results showed that the diffusion coefficients of the drug from vehicles rank according to the following order: Carbopol® 940 gel \((D = 3.11 \times 10^{-7} \pm 0.54 \text{ cm}^2/\text{s}) > \text{chitosan gel} \quad (D = 0.27 \times 10^{-7} \pm 0.08 \text{ cm}^2/\text{s}) > \text{emulsion-based ointment (o/w)} \quad (D = 0.18 \times 10^{-7} \pm 0.05 \text{ cm}^2/\text{s}) > \text{emulsion-based ointment (w/o)} \quad (D = 0.13 \times 10^{-7} \pm 0.05 \text{ cm}^2/\text{s})\).
7 ± 0.02 cm²/s) > hydrophilic petrolatum USP \((D = 0.02 \times 10^{-7} \pm 0.01 \text{ cm}²/\text{s})\). Carbopel® 940 gel base showed significantly higher drug release than the other vehicles \((P < 0.001)\). These results indicated that Carbopel® 940 gel base is a good candidate for the topical delivery of TA

**Santoyo et al. 1995** studied the influence of various penetration enhancers such as urea, dimethyl sulfoxide (DMSO), isopropyl myristate, oleic acid, oleyl alcohol, oleic hexyl ester and linoleic acid on the percutaneous absorption of piroxicam from carbopol gels containing 40% propylene glycol. Skin permeation experiments were carried out using excised abdominal rat skin. Oleic acid was found to be the most efficient penetration enhancer for piroxicam, followed by linoleic acid. With 5% oleic acid, piroxicam flux values increased 8–9-fold compared with control gel.

**Vaddi et al. 2001** made an attempt to enhance the permeation of haloperidol through the rat skin in vitro by using various enhancers at a concentration of 1 mg/ml in the saturated drug solution. The dose-dependent diffusion profile was analysed for the enhancers which significantly increased permeation at this concentration as compared with the control. Enhancers belonging to various chemical classes like the vitamins (ascorbic acid), surfactants (cetrimide, polysorbate 20), sulfoxides (dimethyl sulfoxide), glycols (polyethylene glycol 400, propylene glycol) and amides (urea) were used. Amber glass Franz-type diffusion cells were used for the permeation studies and haloperidol was made soluble in aqueous solution with the aid of lactic acid. Ascorbic acid and cetrimide increased flux and permeability coefficient significantly. From the dose-dependent permeation studies, it was concluded that ascorbic acid enhanced the permeation by increasing the
solubility of the drug in the vehicle thus providing a high concentration gradient across the skin, whereas cetrimide enhanced the permeation by increasing the thermodynamic activity which may be due to solubilization of skin lipids by micelles. Polysorbate 20 decreased the enhancer index by decreasing the thermodynamic activity. None of the enhancers changed the lag time except for urea which decreased the lag time probably by its binding with keratin. Dimethyl sulfoxide, polyethylene glycol 400 and propylene glycol did not have a significant effect on haloperidol permeation when compared with control.

2.7. Plants of interest

The plants of interest are given in table no:2.1 they were selected in consultation with Ayurvedic experts and also based on literature review.

<table>
<thead>
<tr>
<th>Plant Drug</th>
<th>Family Name</th>
<th>Parts Used</th>
<th>Traditional Formulation</th>
<th>Ayurvedic Reference Text</th>
<th>Other References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curcuma longa</td>
<td>Zingibaracea</td>
<td>Rhizome</td>
<td>Nalpamaradikaram, Gulgulmaricha dithy lam</td>
<td>Amobootham, Astangahridayam, Sahasrayogam</td>
<td>62-66</td>
</tr>
<tr>
<td>Azadirea cta indica</td>
<td>Meliaceae</td>
<td>Leaf</td>
<td>Gathyadikaram, Chikilsyamanjari</td>
<td></td>
<td>67-72</td>
</tr>
<tr>
<td>Allium sativum</td>
<td>Liliaceae</td>
<td>Bulb</td>
<td>Neelathulasyadi karam</td>
<td>Jothsiana</td>
<td>72-75</td>
</tr>
<tr>
<td>Cassia fistula</td>
<td>Fabaceae</td>
<td>Leaf</td>
<td>Manibadryagula m</td>
<td>Sahasrayogam</td>
<td>76-80</td>
</tr>
<tr>
<td>Wrightia tinctoria</td>
<td>Apocynaceae</td>
<td>Leaf</td>
<td>-</td>
<td>-</td>
<td>81-85</td>
</tr>
</tbody>
</table>

Table no:2.1.Plants of interest
NEEM 86

Neem consist of dried leaf of *Azadiracta indica* A. Juss

Family : Meliaceae

Synonym : Veppu, Aryaveppu, Nimbam, Veppa

IDENTITY, PURITY AND STRENGTH

Foreign matter : Not more than 2 per cent

Total ash : Not more than 10 per cent

Acid-insoluble ash : Not more than 1 per cent

Alcohol-soluble extractive : Not more than 13 per cent

Water-soluble extractive : Not more than 19 per cent

CONSTITUENTS

Bitter principles Nimbin and Nimbiol

PROPERTIES AND ACTION

Rasa : Tikta

Guna : Laghu, Ruksa

Virya : Sita

Vipaka : Katu
Karma: Kaphahara, Pittahara, Visaghana, Kandughna, Vranasodhanakara, Hrdayavidahasantikara

FORMULATIONS

Nimbadi Kvatha curna, Nimbadi curna, Pancanimba curna, Pancatikta guggulu ghrta, Pathyadi Kwatha (Sadanga) curna, sudersana churna.

THERAPEUTIC USES

Vrana, Kustha, Prameha, Kandu, Krmiroga, Jvara, Daha, Rakta pitta.

DOSE

2-4 g of the drug in powder form, Decoction should be used externally.

TURMERIC

Turmeric consists of the dried and cured rhizomes of *Curcuma longa* Linn.

Family: Zingiberaceae

Synonyms: Manjal

IDENTITY PURITY AND STRENGTH

Identity

1. On the addition of concentrated sulphuric acid or a mixture of concentrated sulphuric acid and alcohol to the powdered drug, a deep crimson colour is produced.
2. A piece of filter paper is impregnated with an alcoholic extract of powder, dried and then moistened with a solution of Boric acid slightly acidified with Hydrochloric acid and dried again. The filter paper assumes a pink or
brownish red colour which becomes deep blue or greenish black on the addition of alkali.

Foreign matter: Not more than 0.9 per cent

Total ash: Not more than 9 per cent

Acid-insoluble ash: Not more than 1 per cent

Alcohol-soluble extractive: Not more than 8 per cent

Water soluble extractive: Not more than 12 per cent

Volatile oil: Not more than 4 per cent

CONSTITUENTS

Essential oil and colouring matter (Curcumin)

PROPERTIES

Rasa: Titka, Kata

Guna: Ruksa

Virya: Ushna

Vipaka: Katu

Karma: Kaphapittanal, Visashna, Kusthagham, Krimighna, Pramehanasaka

FORMULATIONS

Haridra, Khanda
THERAPEUTIC USES

Visavikara, Kastha varna, Tragroga, Prameha, Pandu, sitapitta, pinasa

DOSE

1-3 g drug in powder form

GARLIC86

Garlic consists of bulb of *Allium sativum* Linn.

Family : Liliaceae

Synonyms : Vellulli, Nelluthulli

Foreign matter : Not more than 2 per cent

Total ash : Not more than 4 per cent

Acid insoluble ash : Not more than 1 per cent

Alcohol soluble extractive : Not more than 2.5 per cent

Loss on drying : Not more than 60 per cent

Volatile oil : Not more than 0.1 per cent

TLC

TLC of alcoholic extract on silica gel on silica gel ‘G’ plate using n-Butanol: Isopropanol: Acetic acid: water (3:1:1:1) shows under UV (366 nm) two fluorescent zone at Rf 0.58 and 0.72 (both light blue). On exposure to iodine vapour nine spots appear at Rf 0.18, 0.26, 0.34, 0.38, 0.46, 0.58, 0.72, 0.77 and 0.93 (all yellow). On spraying with Ninhydrin reagent and heating the plate for ten minutes at 1100°C
seven spots appear at Rf 0.26, 0.38, 0.46, 0.58, 0.67, 0.72 and 0.93 (all pink). On spraying with vanillin-sulphuric acid reagent and heating the plate for 10 minutes at 1100°C seven spots appear at Rf 0.26, 0.38, 0.46, 0.58, 0.67, 0.72 and 0.93 (all grey)

CONSTITUENTS

Volatile oil containing Allyl Disulphide and Diallyl Disulphide. It also contains Allin, allicin, mucilage and albumin

PROPERTIES AND ACTION

Rasa : Katu, Madhura

Guna : Guru, Snigdha, Tiksna, Sara, Picchila

Virya : Usna

Vipaka : Katu

Karma : Vatahara, Kaphahara, Pita dusanakara, Raktadosahara, Bhagnasandhanakara, Dipana, Rasayena, Balya, Hrdya, Vrsya, Varnya, Medhya, Jantughna, Kanthya, Asthi mamsa sandhankar, Caksusya

FORMULATIONS

Lasunadi Vati, Lasunadi Ghrta and Vaca Lasunadi Taila

THERAPEUTIC USES

Jirna, Jwara, Krmiroga, Gulma, Kustha, Arsa, Kasa, Swasa, Pinas, Sula, Karnasula, Vatavyadhi, Hikka, Medoroga, Yoni vyapata, Visucika, Pliha vrdhhi,
Ksaya, Visama jwara, Apasmara, Unmada, Sasa, Sopha, Hrdroga, Vatsula, Trikasula,
Vrana krimi

DOSE

3 g of the drug

KANIKONNA 86

Kanikonna consists of dried leaves of *Cassia fistula* Linn.

Family : Leguminosae

Synonyms : Konna, Kritamalam

IDENTITY, PURITY AND STRENGTH

Foreign matter : Not more than 2 per cent

Total ash : Not more than 6 per cent

Acid insoluble ash : Not more than 1 per cent

Alcohol soluble extractive : Not more than 15 per cent

Water-soluble extractive : Not more than 46 per cent

CONSTITUENTS

Sugar, mucilage, pectin and Anthraquinone

PROPERTIES AND ACTION

Rasa : Madhura, Tikta

Guna : Guru
Virya : Usna
Vipaka : Madhura
Karma : Recana

FORMULATIONS

Aragvadhadi kvatha curna

THERAPEUTIC USES

Vibandha, Udavartta, Gulma, Sula, Udararoga, Hrdroga, Prameha.

DOSE

5-10 g of the drug in powder form

PALA INDIGO PLANT

Pala indigo plant consists of leaves, bark and seeds of Wrightia tinctoria (Roxb.)

Family : Apocynaceae

Synonyms : Dantappala, Ayyappala, Tinnampala

THERAPEUTIC USES

The leaves are acrid, thermogesic, hypotensive, and are useful in odontalgia, vitiated conditions of vata and hypertension. The bark and seeds are bitter, astringent, acrid, thermogenic, carminative, digestive, constipating, depurative, anthelminthie, aphrodisiac and febrifuge. They are also useful in vitiated conditions of pitta and kapha, dyspepsia, flatulence, colic, diarrhoea, leprosy, psoriasis, haemorrhoids,
helminthiasis, fever, burning sensation and dropsy. The latex of the bark and unripe fruits are used by hill tribes for coagulating and solidifying milk.

2.8. Drugs and Formulations of interest

**Chrysophanic acid**

<table>
<thead>
<tr>
<th>Name</th>
<th>Chrysophanic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synonyms</td>
<td>Chrysophanol; 1,8-Dihydroxy-3-methylanthraquinone</td>
</tr>
<tr>
<td>Molecular Structure</td>
<td><img src="image" alt="Molecular Structure Diagram" /></td>
</tr>
<tr>
<td>Molecular Formula</td>
<td>C₁₅H₁₀O₄</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>254.24</td>
</tr>
<tr>
<td>CAS Registry Number</td>
<td>481-74-3</td>
</tr>
<tr>
<td>Melting point</td>
<td>194-198 °C</td>
</tr>
<tr>
<td>Water solubility</td>
<td>&lt;0.1 g/100 ml at 18 °C</td>
</tr>
</tbody>
</table>

**Method of Analysis**

Various methods have been reported in the literature for the analysis of Chrysophanol including thin layer chromatography scanning (TLCS)⁸⁷, High Performance Liquid Chromatography (HPLC) with UV–Vis detection⁸⁸, PDA detection⁸⁹,⁹⁰ or MS/MS detection⁹¹, capillary electrophoresis with UV–Vis
detection\textsuperscript{92,93} or electrochemical detection\textsuperscript{94,95} However, there were no reports on simple validated UV Spectrophotometric method for estimation of Chrysophanol.

**Gentamicin Sulfate Ointment USP, 0.1\%**

For Dermatologic Use

Description

Gentamicin Sulfate Ointment is a wide spectrum antibiotic preparation for topical application. Each gram contains 1.0 mg of Gentamicin in a base of White Petrolatum with Methylparaben and Propylparaben as preservatives.

Clinical Pharmacology

Gentamicin sulfate is a wide spectrum antibiotic that provides highly effective topical treatment in primary and secondary bacterial infections of the skin. Gentamicin sulfate ointment may clear infections that have not responded to treatment with other topical antibiotic agents. In primary skin infections such as impetigo contagiosa, treatment for 3 or 4 times daily with Gentamicin sulfate ointment usually clears the lesions promptly. In secondary infections, Gentamicin sulfate ointment aids in the treatment of the underlying dermatoses by controlling the infection. Bacteria susceptible to the action of gentamicin sulfate include sensitive strains of *Streptococci (group A beta-hemolytic, alpha-hemolytic)*, *Staphylococcus aureus (coagulase positive, coagulase negative, and some penicillinase-producing strains)*, and the gram-negative bacteria, *Pseudomonas aeruginosa, Aerobacter aerogenes, Escherichia coli, Proteus vulgaris, and Kiebsiella pneumoniae*. 
Indications and Usage

Primary skin infections: Impetigo contagiosa, superficial folliculitis, eczema, furunculosis, sycosis barbae, and pyoderma gangrenosum. Secondary skin infections: Infectious eczematoid dermatitis, pustular acne, pustular psoriasis, infected seborrheic dermatitis, infected contact dermatitis, infected excoriations, and bacterial super-infections of fungal or viral infections. Gentamicin sulfate is useful in the treatment of infected skin cysts and certain other skin abscesses when preceded by incision and drainage to permit adequate contact between the antibiotic and the infecting bacteria. Good results have been obtained in the treatment of infected stasis and other skin ulcers, infected superficial burns, infected insect bites and stings, infected lacerations and abrasions, and wounds from minor surgery. Gentamicin sulfate ointment may be used in children over one year of age as well as in adults.

Mechanisam of Action

Aminoglycosides disrupt the normal cycle of ribosomal function by interfering, at least in part, with the initiation of protein synthesis, leading to the accumulation of abnormal initiation complexes. Aminoglycosides also cause misreading of the mRNA template and incorporation of incorrect amino acids into the growing polypeptide chains. Aminoglycosides vary in their capacity to cause misreading presumably owing to differences in their affinities for specific ribosomal proteins. Although there appears to be a strong correlation between bactericidal activity and the ability to induce misreading, it remains to be established that this is the primary mechanism of aminoglycoside-induced cell death.
Neosporin skin ointment

Neosporin is the product name of an antibiotic ointment produced by GSK (Glaxo Smithkline Pharmaceuticals limited) used in the prevention of infection and speeding the healing of wounds. This product is approved by US-FDA. The original ointment contains three different antibiotics: bacitracin, neomycin, and polymyxin B, and each gram of the ointment contains:

- PolymyxinB Sulphate USP 5000 units
- Bacitracine zinc IP 400 units
- Neomycin sulphate 3400 units

**Polymyxin B Sulfate**

Polymyxin B sulfate is the sulfate salt of polymyxin B<sub>1</sub> and B<sub>2</sub> which are produced by the growth of *Bacillus polymyxa*. 
Neomycin Sulfate

Neomycin sulfate is the sulfate salt of neomycin B and C, which are produced by the growth of *Streptomyces fradiae*.

Bacitracin

Bacitracin is the polypeptide produced by *Bacillus subtilis*. Inhibits regeneration of phospholipids receptors involved in peptidoglycan synthesis. Active against gram positive and negative organisms.

Clinical Pharmacology

The anti-infective components in the combination are included to provide action against specific organisms susceptible to them. Polymyxin B sulfate and neomycin sulfate together are considered to be active against the following microorganisms: *Staphylococcus aureus, Escherichia coli, Haemophilus influenzae, Klebsiella-Enterobacter species*, *Neisseria* species and *Pseudomonas aeruginosa*. Bacitracin is active against most Gram-positive bacteria, pathogenic *Neisseria spp* and *Haemophilus influenzae*. Bacitracin is active against gram positive and negative organisms.